The Olefin Metathesis Approach to Epothilone A and Its Analogues

K. C. Nicolaou,* Y. He, D. Vourloumis, H. Vallberg, F. Roschangar, F. Sarabia, S. Ninkovic, Z. Yang, and J. I. Trujillo

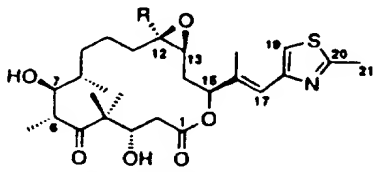
Contribution from the Department of Chemistry and The Skaggs Institute for Chemical Biology and The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, and Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093

Received April 7, 1997[⊗]

Abstract: The olefin metathesis approach to epothilone A (**1**) and several analogues (**39**–**41**, **42**–**44**, **51**–**57**, **58**–**60**, **64**–**65**, and **67**–**69**) is described. Key building blocks **6**–**8** were constructed in optically active form and were coupled and elaborated to olefin metathesis precursor **4** via an aldol reaction and an esterification coupling. Olefin metathesis of compound **4**, under the catalytic influence of $RuCl_2(=CHPh)(PCy_3)_2$, furnished *cis*- and *trans*-cyclic olefins **3** and **48**. Epoxidation of **49** gave epothilone A (**1**) and several analogues, whereas epoxidation of **50** resulted in additional epothilones. Similar elaboration of isomeric as well as simpler intermediates resulted in yet another series of epothilone analogues and model systems.

1. Introduction

The epothilones (A: **1** and B: **2**, Figure 1)[1-4] represent a new class of natural products with potent microtubule binding and stabilizing abilities and selective antitumor properties.[3,4] In their action as inducers of tubulin polymerization and microtubule stabilization, the epothilones resemble Taxol,[5,6] which they do not only mimic but also displace on the microtubules.[3,4] Significantly, these new antitumor agents exhibit selective cytotoxicity and are particularly effective against certain drug-resistant tumor cell lines, even in cases where Taxol fails.[3,4] Epothilones A (**1**) and B (**2**) were originally isolated by Höfle et al. from myxobacteria (*Sorangium cellulosum* strain 90)[1,2] and independently by a group at Merck.[4a] Their novel molecular architecture has been fully characterized by spectroscopic and X-ray crystallographic techniques.[2] Their structural appeal combined with their important biological activities[3,4] and intriguing mechanism of action[4] defines exciting opportunities for synthetic chemists, biologists, and clinicians.[7-12] Our interest focused initially on developing strategies for the total synthesis of these natural substances and of designed epothilones for chemical and biological studies.[7a,10,11] In this article, we describe the details of our olefin metathesis approach to epothilone A (**1**) and its application to the synthesis of several of its analogues. Similar strategies leading to total syntheses of epothilone A (**1**) and several of its congeners were independently pursued by the Danishefsky[9] and the Schinzer groups.[12] The first total synthesis of epothilone A was achieved via an intramolecular ester enolate–aldehyde condensation by the Danishefsky group.[8]



1: R = H, epothilone A
2: R = Me, epothilone B

Figure 1. Structure and numbering of epothilones A (**1**) and B (**2**).

2. Retrosynthetic Analysis and Strategy

The structure of epothilone A (**1**) is characterized by a 16-membered macrocyclic lactone carrying a *cis*-epoxide moiety, two hydroxyl groups, two secondary methyl groups, and a *gem* dimethyl group, as well as a side chain consisting of a trisubstituted double bond and a thiazole moiety. With its seven stereocenters and two geometrical elements, epothilone A (**1**) presents a considerable challenge as a synthetic target, particularly with regard to stereochemistry and functional group

[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1997.

(1) (a) Höfle, G.; Bedorf, N.; Gerth, K.; Reichenbach, H. (GBF) DE-4138042, 1993 (*Chem. Abstr.* **1993**, *120*, 52841). (b) Gerth, K.; Bedorf, N.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot.* **1996**, *49*, 560–563.

(2) Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, G.; Reichenbach, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1567–1569.

(3) Grever, M. R.; Schepartz, S. A.; Chabner, B. A. *Semin. Oncol.* **1992**, *19*, 622–638.

(4) (a) Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res.* **1995**, *55*, 2325–2333. (b) Kowalski, R. J.; Giannakakou, P.; Hamel, E. *J. Biol. Chem.* **1997**, *272*, 2534–2541.

(5) Horwitz, S. B.; Fant, J.; Schiff, P. B. *Nature* **1979**, *277*, 665–667.

(6) Nicolaou, K. C.; Dai, W.-M., Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15–44.

(7) (a) Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Yang, Z. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2399–2401. (b) Meng, D.; Sorensen, E. J.; Bertinato, P.; Danishefsky, S. J. *J. Org. Chem.* **1996**, *61*, 7998–7999. (c) Bertinato, P.; Sorensen, E. J.; Meng, D.; Danishefsky, S. J. *J. Org. Chem.* **1996**, *61*, 8000–8001. (d) Schinzer, D.; Limberg, A.; Böhm, O. M. *Chem. Eur. J.* **1996**, *2*, 1477–1482. (e) Mulzer, J.; Mantoulidis, A. *Tetrahedron Lett.* **1996**, *37*, 9179–9182. (f) Claus, E.; Pahl, A.; Jones, P. G.; Meyer, H. M.; Kalesse, M. *Tetrahedron Lett.* **1997**, *38*, 1359–1362. (g) Gabriel, T.; Wessjohann, L. *Tetrahedron Lett.* **1997**, *38*, 1363–1366. (h) Taylor, R. E.; Haley, J. D. *Tetrahedron Lett.* **1997**, *38*, 2061–2064.

(8) Balog, A.; Meng, D.; Kamenecka, T.; Bertinato, P.; Su, D.-S.; Sorensen, E. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2801–2803.

(9) Meng, D.; Su, D.-S.; Balog, A.; Bertinato, P.; Sorensen, E. J.; Danishefsky, S. D.; Zheng, Y.-H.; Chou, T.-C.; He, L.; Horwitz, S. B. *J. Am. Chem. Soc.* **1997**, *119*, 2733–2734.

(10) Yang, Z.; He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 166–168.

(11) Nicolaou, K. C.; Sarabia, F.; Ninkovic, S.; Yang, Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 525–527.

(12) Schinzer, D.; Limberg, A.; Bauer, A.; Böhm, O. M.; Cordes, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 523–524.

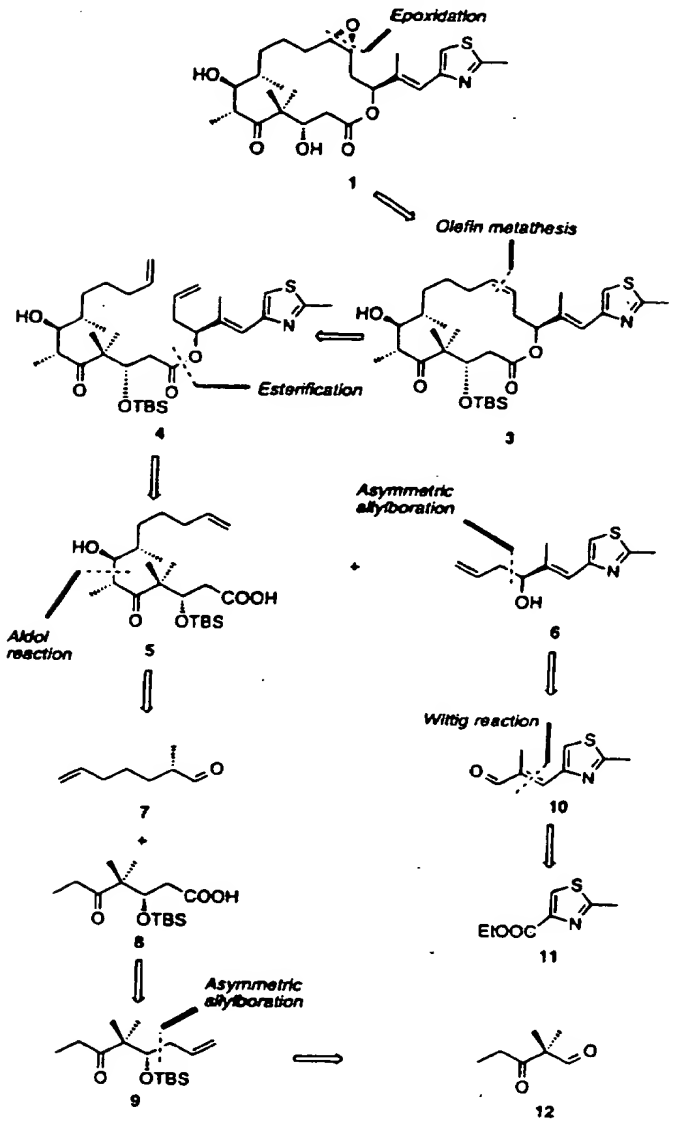
S0002-7863(97)01109-8 CCC: $14.00

sensitivity. In search for a suitable synthetic strategy, we sought to apply new principles of organic synthesis and, at the same time, retain optimum flexibility for structural diversity and construction of libraries.

In recent years, the olefin metathesis reaction has become a powerful tool for organic synthesis.[13] In particular, a number of publications report application of this chemistry to the construction of macrocycles.[14]

Inspection of the structure of epothilone A (**1**) revealed the intriguing possibility of applying the olefin metathesis reaction to bis(terminal) olefin **4** to yield the *cis*-olefin-containing macrocyclic lactone **3**, which could be converted to the natural product by simple epoxidation, as retrosynthetically outlined in Scheme 1. Daring as it was, this strategy had the potential of delivering both the *cis*- and *trans*-cyclic olefins corresponding to **4** for structural variation. Proceeding with the retrosynthetic analysis, an esterification reaction was identified as a means to permit disconnection of **4** to its components, carboxylic acid **5** and secondary alcohol **6**. The aldol moiety in **5** allowed the indicated disconnection, defining aldehyde **7** and keto acid **8** as potential intermediates. Carboxylic acid **8** could then be traced to intermediate **9**, whose asymmetric synthesis via allylboration of the known keto aldehyde **12** was straightforward. An asymmetric allylboration could also be envisioned as a method to construct alcohol **6**, leading to precursor **10**, which could be derived from the known thiazole derivative **11**. This retrosynthetic analysis led to a highly convergent and flexible synthetic strategy, the execution of which proved to be highly rewarding in terms of delivering epothilone A (**1**) and a series of analogues of this naturally occurring substance for biological screening.

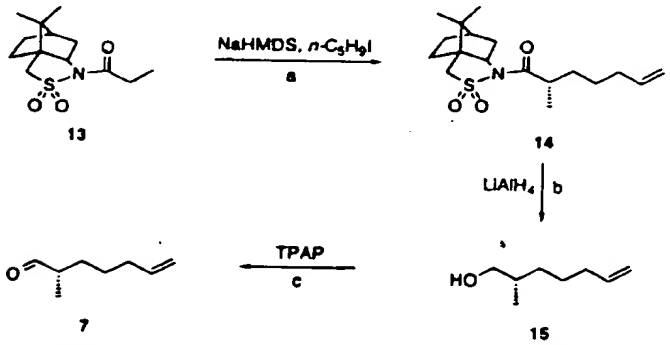
Scheme 1. Retrosynthetic Analysis of Epothilone A (**1**)



3. Construction of Key Building Blocks and Model Studies

As a prelude to the total synthesis, a number of building blocks were synthesized and utilized in model studies. Thus, fragments **7**, **18a,b**, and **21** (Schemes 2–4) were targeted for synthesis. Aldehyde **7** was constructed by two different routes, one of which is summarized in Scheme 2.[15] Thus, Oppolzer's acylated sultam derivative **13**[16] was alkylated with 5-iodo-1-pentene in the presence of sodium bis(trimethylsilyl)amide (NaHMDS) to furnish compound **14** as a single diastereoisomer (by ^{1}H NMR). Lithium aluminum hydride reduction of **14** produced alcohol **15**[14d] in 60% overall yield from sultam **13**. Oxidation of **15** with tetrapropylammonium perruthenate(VII) (TPAP)[17] and 4-methylmorpholine *N*-oxide (NMO) provided the desired aldehyde **7** in 95% yield.

Scheme 2. Synthesis of Aldehyde **7**[a]



[a] Reagents and conditions: (a) 1.05 equiv of NaHMDS, 2.0 equiv of n-C_5H_9I, 3.0 equiv HMPA, −78 → 25 °C, 5 h; (b) 1.1 equiv of $LiAlH_4$, THF, −78 °C, 15 min, 60% (two steps); (c) 1.5 equiv of NMO, 5 mol % of TPAP, CH_2Cl_2, 4 Å MS, 25 °C, 0.5 h, 95%. NaHMDS = sodium bis(trimethylsilyl)amide; HMPA = hexamethylphosphoramide. NMO = 4-methylmorpholine *N*-oxide; TPAP = tetrapropylammonium perruthenate.

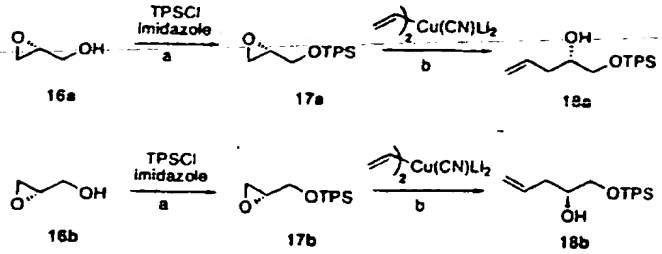
(13) For the development of the olefin metathesis as a ring forming reaction, see: (a) Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634–6640. (b) Schwab, P. R.; Grubbs, H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110. (c) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446–452 and references therein. (d) Tsuji, J.; Hashiguchi, S. *Tetrahedron Lett.* **1980**, *21*, 2955–2959. For some earlier pioneering studies on this reaction, see: (e) Katz, T. J.; Lee, S. J.; Acton, N. *Tetrahedron Lett.* **1976**, 4247–4250. (f) Katz, T. J.; Acton, N. *Tetrahedron Lett.* **1976**, 4241–4254. (g) Katz, T. J.; McGinnis, J.; Altus, C. *J. Am. Chem. Soc.* **1976**, *98*, 606–608. (h) Katz, T. J. *Adv. Organomet. Chem.* **1977**, *16*, 283–317.

(14) For a number of applications of the olefin metathesis reaction in medium and large ring synthesis, see: (a) Borer, B. C.; Deerenberg, S.; Bieräugel, H.; Pandit, U. K. *Tetrahedron Lett.* **1994**, *35*, 3191–3194. (b) Clark, T. D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1995**, *117*, 12364–12365. (c) Houri, A. F.; Xu, Z.; Cogan, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943–2944. (d) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942–3943. (e) Martin, S. F.; Chen, H.-J.; Courtney, A. K.; Liao, Y.; Pätzel, M.; Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251–7264. (f) Xu, Z.; Johannes, C. W.; Salman, S. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 10926–10927.

(15) For the other route to **7**, see ref 7a.

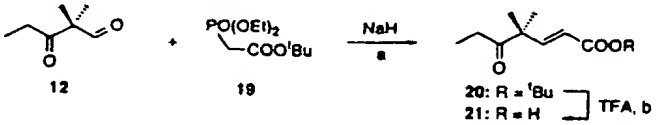
(16) (a) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603–1989. (b) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241–1250.

Scheme 3. Synthesis of Alcohols **18a,b**[a]



[a] Reagents and conditions: (a) 1.3 equiv of TPSCl, 2.0 equiv of imidazole, DMF, 0 → 25 °C, 1.5 h (90% of **17a**, 94% of **74b**); (b) 1.25 equiv of tetravinyltin, 5.0 equiv of *n*-BuLi, THF, −78 °C, 45 min, then 2.5 equiv of CuCN in THF, −78 → −30 °C; then **17a** or **17b** in THF, −30 °C, 1 h, **18a** (86%), **18b** (83%). TPS = $SiPh_2{}^tBu$.

Scheme 4. Synthesis of Ketoacid **21**[a]



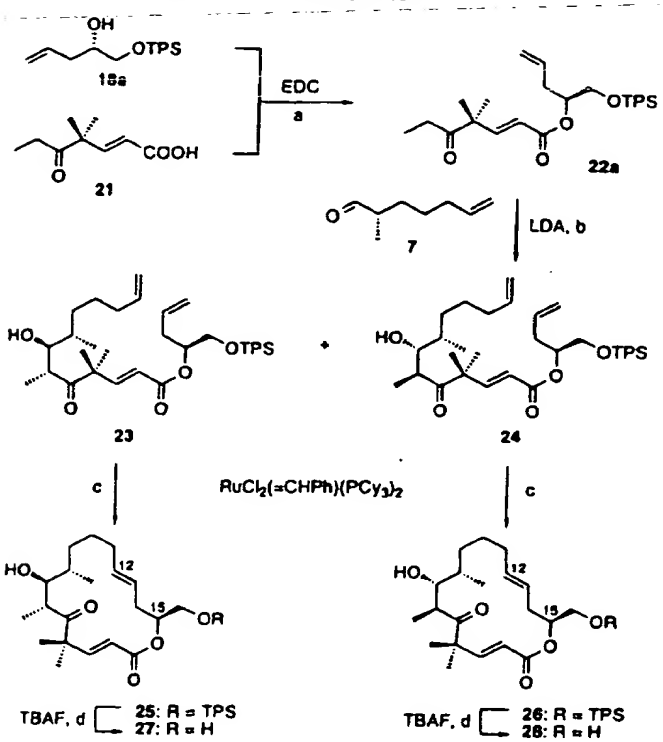
[a] Reagents and conditions: (a) 1.2 equiv of **19**, 1.6 equiv of NaH, THF, 0 → 25 °C, 1 h, 99%; (b) CF_3COOH (TFA):CH_2Cl_2 (1:1), 25 °C, 0.5 h, 99%.

The synthesis of the two antipodal alcohols **18a,b** is outlined in Scheme 3. Thus, glycidols **16a** and **16b** were converted to the corresponding *tert*-butyldiphenylsilyl ethers (OTPS) **17a** (90% yield) and **17b** (94% yield), respectively, by a standard procedure (TPSCl, imidazole), and then to homoallylic alcohols **18a** (86% yield) and **18b** (83% yield) by reaction with the vinyl cuprate reagent derived from copper(I) cyanide and vinyllithium.[18]

Scheme 4 summarizes the synthesis of the third required building block, keto acid **21**, starting with the known and readily available keto aldehyde **12**.[19] Condensation of **12** with the sodium salt of phosphonate **19** produced α,β-unsaturated ester **20** in 99% yield. Cleavage of the *tert*-butyl ester with CF_3-COOH (TFA) in CH_2Cl_2 resulted in a 99% yield of carboxylic acid **21**.

With the requisite fragments in hand, we turned our attention to a feasibility study of the olefin metathesis strategy. Scheme 5 summarizes the results of our initial work in this field. Thus, coupling of fragments **18a** and **21**, mediated by the action of 1-ethyl-(3-(dimethylamino)propyl)-3-carbodiimide hydrochloride (EDC) and 4-dimethylaminopyridine (4-DMAP), led to ester **22a** in 86% yield. Aldol condensation of the lithium enolate of keto ester **22a** (generated by the action of lithium diisopropylamide (LDA)) and aldehyde **7** resulted in the formation of aldols **23** and **24** in ca. 4:3 ratio (^{1}H NMR). Chromatographic separation allowed the isolation of pure **23** (42% yield) and **24** (33% yield). The stereochemical assignments of compounds **23** and **24** were based on an X-ray crystallographic analysis of a subsequent intermediate as will be described below. Returning to Scheme 5, exposure of **23** to the $RuCl_2(=CHPh)(PCy_3)_2$ catalyst in CH_2Cl_2 solution under high-dilution conditions at 25 °C for 12 h resulted in clean formation of single *trans*-macrocyclic olefin **25** ($J_{12,13}$ = 15.5 Hz) in 85% yield. Similar treatment of **24** generated the diastereomeric *trans*-olefin **26** ($J_{12,13}$ = 15.2 Hz) as the sole product in 79% yield. Desilylation of **25** and **26** with tetrabutylammonium fluoride (TBAF) and AcOH in THF at 25 °C furnished dihydroxy lactones **27** (92% yield) and **28** (95% yield, mp 128−129 °C, EtOAc−hexanes), respectively.

Scheme 5. Synthesis of the Epothilone Cyclic Framework via Olefin Metathesis: the 15*S* Series[a]



[a] Reagents and conditions: (a) 1.2 equiv of EDC, 0.1 equiv of 4-DMAP, CH_2Cl_2, 0 → 25 °C, 12 h, 86%; (b) **21**, 1.2 equiv of LDA, −78 °C → 40 °C, THF, 45 min; then 1.6 equiv of **7** in THF, −78 → −40 °C, 0.5 h, **23** (42%), **24** (33%); (c) 0.1 equiv of $RuCl_2$-(=CHPh)$(PCy_3)_2$, CH_2Cl_2, 25 °C, 12 h, **25** (85%), **26** (79%); (d) 2.0 equiv of TBAF, 5.0 equiv of AcOH, 25 °C, 36 h, **27** (92%), **28** (95%). EDC = 1-ethyl-3-(3-(dimethylamino)propyl-3-carbodiimide hydrochloride. 4-DMAP = 4-dimethylaminopyridine. LDA = lithium diisopropylamide. TBAF = tetrabutylammonium fluoride.

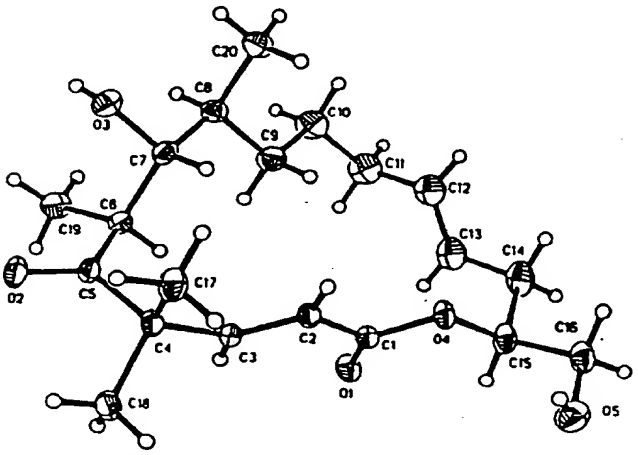
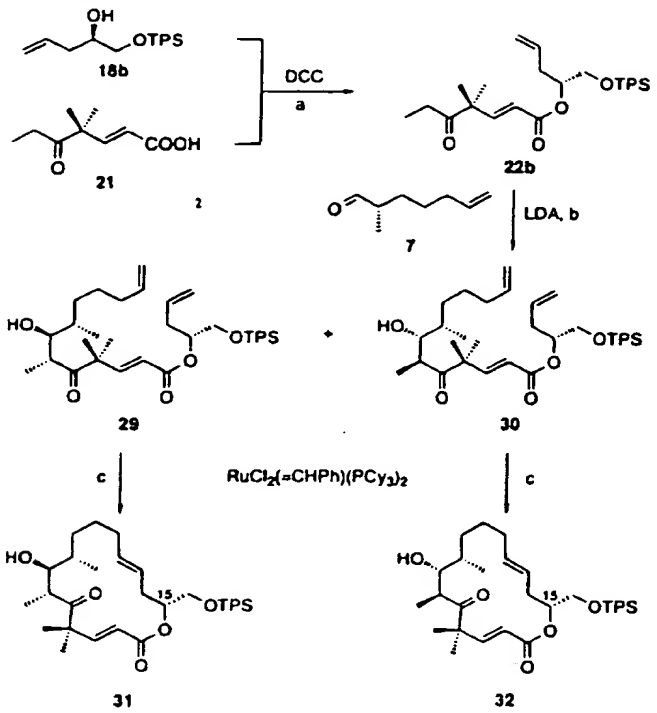


Figure 2. ORTEP drawing of compound **28**.

X-ray crystallographic analysis of macrocyclic diol **28** revealed the *trans* nature of the double bond and defined the stereochemistry of all stereogenic centers (see ORTEP drawing of compound **28**, Figure 2). Comparison of the ^{1}H NMR spectra of **26** and **28** with those of **25** ($J_{12,13}$ = 15.5 Hz), **27**, **31** ($J_{12,13}$ = 15.7 Hz) and **32** (vide infra) supported the *trans* geometry

(17) Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13−19.
(18) Lipshutz, B. H.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 1147−1149.
(19) Inuka, T.; Yoshizawa, R. *J. Org. Chem.* **1967**, *32*, 404−407.

Scheme 6. Synthesis of the Epothilone Cyclic Framework via Olefin Metathesis: the 15*R* Series[a]



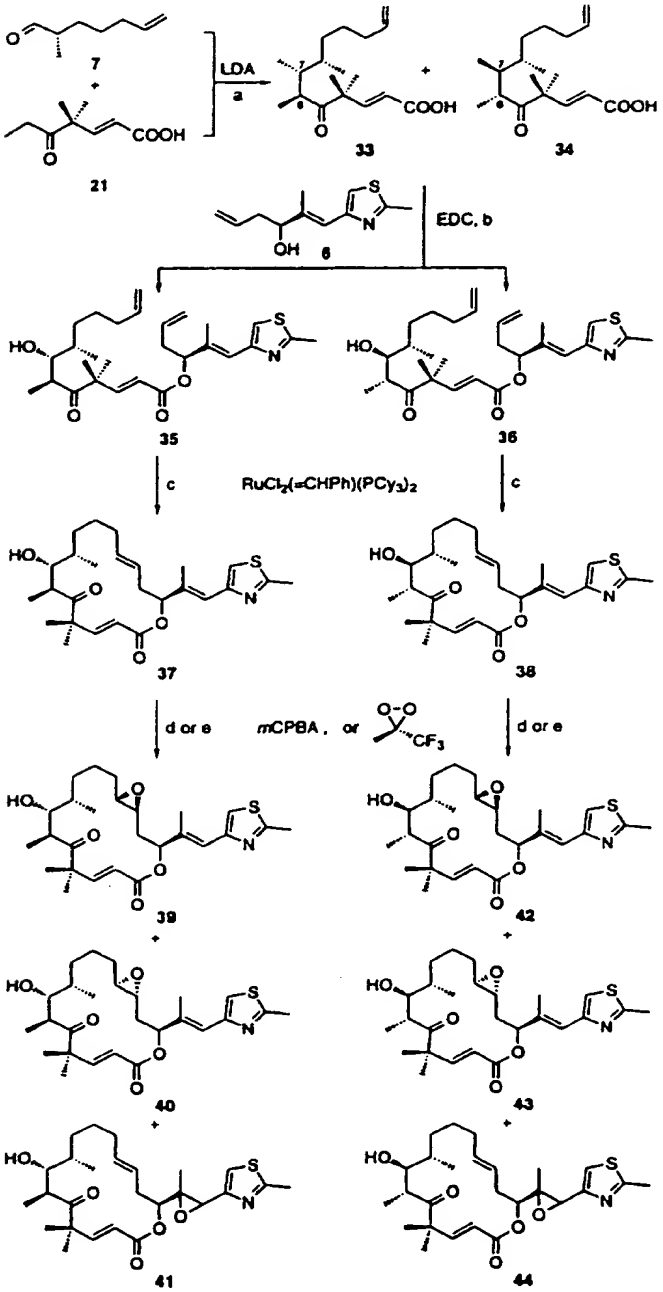
[a] Reagents and conditions: (a) 1.4 equiv of DCC, 1.4 equiv of 4-DMAP, toluene, 25 °C, 12 h, 95%; (b) **21**, 1.2 equiv of LDA, −78 °C → −40 °C, THF, 45 min; then 1.6 equiv of **7** in THF, −78 → −40 °C, 0.5 h, **29** (54%), **30** (24%); (c) 0.1 equiv of $RuCl_2(=CHPh)(PCy_3)_2$, CH_2Cl_2, 25 °C, 12 h, **31** (80%), **32** (81%). DCC = 1,3 dicyclohexylcarbodiimide.

of the double bond generated by the olefin metathesis and the C6−C7 stereochemistry. Therefore, the original assignment[7a] of the *cis* geometry for this double bond and the C6−C7 stereochemistry of the aldol products in these model systems should now be revised as shown. Ironically, it was this erroneous, but encouraging, assignment that led us to embark on the final plan to synthesize epothilone A by the olefin metathesis approach. As events unfolded (vide infra), the real system produced both the *cis*- and the *trans*-cyclic olefins and the metathesis approach turned out to be fruitful.

For the purposes of analogue synthesis, the 15*R*-fragment **18b** was also utilized in these studies, as shown in Scheme 6. Coupling of **18b** and **21** with 1,3-dicyclohexylcarbodiimide (DCC) and 4-DMAP led to a 95% yield of ester **22b**, the enantiomer of **22a**. LDA-mediated aldol condensation of **22b** with aldehyde **7** furnished aldols **29** (54% yield) and **30** (24% yield), which are diastereomeric with **23** and **24** of Scheme 5. Olefin metathesis of **29** and **30** with the $RuCl_2(=CHPh)(PCy_3)_2$ catalyst led to cyclic systems **31** ($J_{12,13}$ = 15.7 Hz) (80% yield) and **32** ($J_{12,13}$ = 15.4 Hz) (81% yield), respectively. Compounds **27**, **28**, **31**, and **32** may serve as suitable precursors for the construction of a series of designed epothilones for biological investigations. At this juncture, however, it was considered more urgent to investigate the compatibility of the thiazole side chain with the conditions of olefin metathesis and epoxidation.

To this end, the chemistry shown in Scheme 7 was studied. The enolate of keto acid **21** (2.3 equiv of LDA, THF, −78 → −30 °C) reacted with aldehyde **7** to afford hydroxy acids **33** and **34** as a mixture of C6−C7 diastereomers (ca. 2:3 by ^1H NMR) in good yield. This mixture was coupled with alcohol

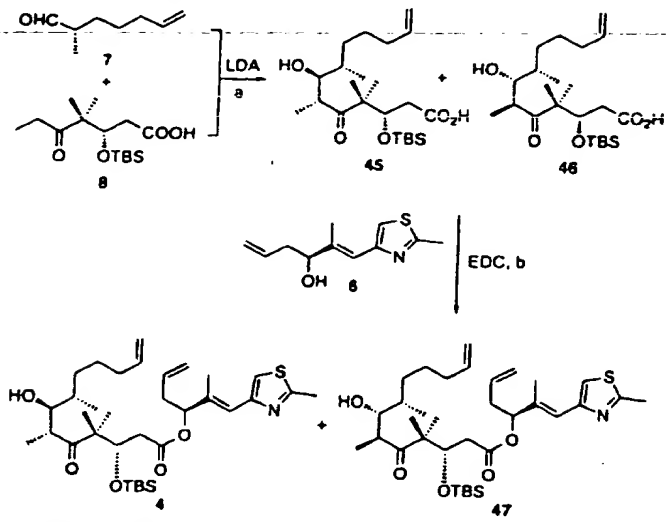
Scheme 7. Metathesis and Epoxidation in the Presence of Thiazole: Synthesis of Epothilone Analogues **39**−**44**[a]



[a] Reagents and conditions: (a) **21**, 2.3 equiv of LDA, −78 → −30 °C, THF, 1.5 h; then 1.6 equiv of **7** in THF, −78 → −40 °C, 1 h (**33**:**34**, 2:3); (b) ca. 2.0 equiv of **6**, ca. 1.2 equiv of EDC, ca. 0.1 equiv of 4-DMAP, CH_2Cl_2, 0 → 25 °C, 12 h, **35** (29%), **6** (44%) (two steps); (c) 0.1 equiv of $RuCl_2(=CHPh)(PCy_3)_2$, CH_2Cl_2, 25 °C, 12 h, **37** (86%), **38** (66%); (d) 0.9−1.2 equiv of *m*CPBA, $CHCl_3$, −20 → 0 °C, 12 h, **37** → **39** (or **40**) (40%), **40** (or **39**) (25%), **41** (18%); **38** → **42** (or **43**) (22%), **43** (or **42**) (11%), **44** (7%); (e) excess of CF_3COCH_3, 8.0 equiv of $NaHCO_3$, 5.0 equiv of Oxone, CH_3CN/Na_2EDTA (2:1), 0 °C, **37** → **39** (or **40**) (45%), **40** (or **39**) (28%); **38** → **42** (or **43**) (60%), **43** (or **42**) (15%). *m*CPBA = 3-chloroperoxybenzoic acid. Oxone = potassium peroxymonosulfate. Na_2EDTA = ethylenediaminetetraacetic acid disodium salt.

6[20] in the presence of EDC and 4-DMAP to afford two diastereomeric esters **35** and **36** (29% and 44% yield, respectively, for two steps). Both products, **35** and **36**, were subjected to the olefin metathesis reaction, and we were delighted to

Scheme 8. Coupling of Building Blocks 6–8[a]



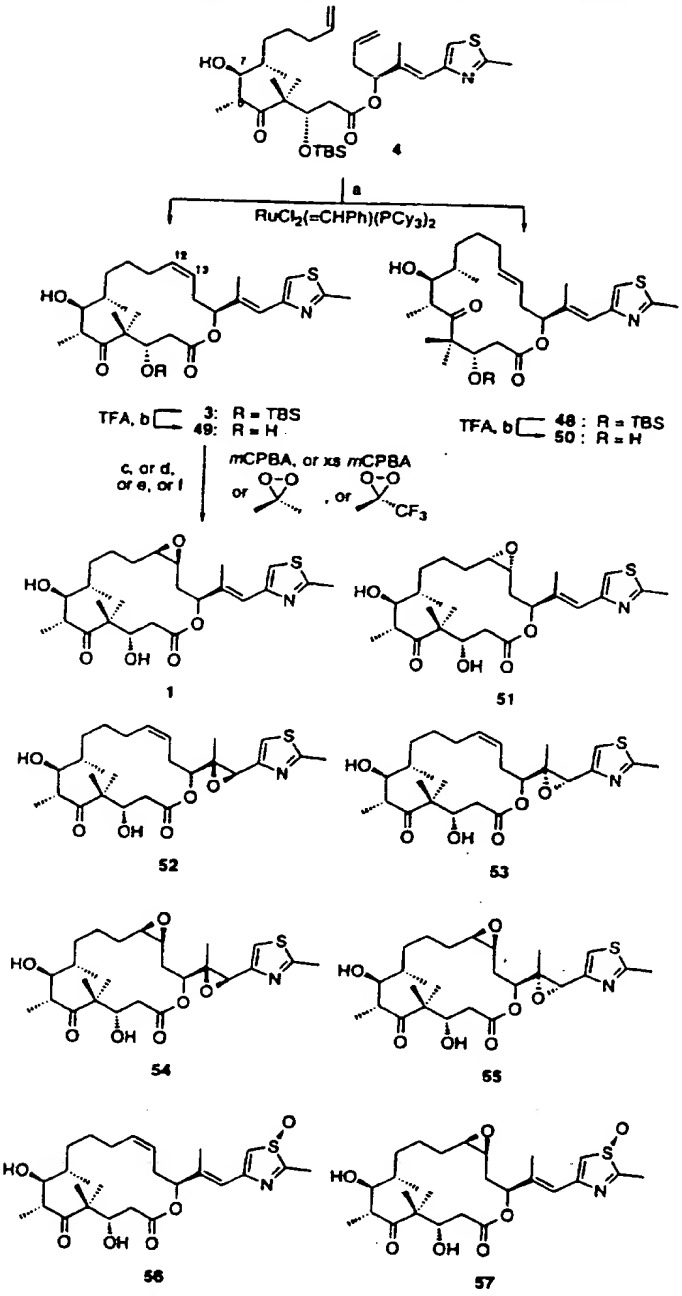
[a] Reagents and conditions: (a) **8**, 2.3 equiv of LDA, −78 → −30 °C, THF, 1.5 h; then 1.6 equiv of **7** in THF, −78 → −40 °C, 1 h (45:46, 3:2); (b) ca. 2.0 equiv of **6**, ca. 1.2 equiv of EDC, ca. 0.1 equiv of 4-DMAP, CH_2Cl_2, 0 → 25 °C, 12 h, **4** (52%), **47** (31%) (two steps).

observe a smooth ring closure leading to *trans*-macrocycles **37** ($J_{12,13}$ = 15.5 Hz) (86%) and **38** ($J_{12,13}$ = 15.0 Hz) (66%). With cyclized products **37** and **38** in hand, we then proceeded to demonstrate the feasibility of epoxidizing the C12–C13 double bond in the presence of the thiazole and olefin functionalities in the side chain. Thus, treatment of both **37** and **38** with 0.9–1.2 equiv of 3-chloroperoxybenzoic acid (*m*CPBA) in $CHCl_3$ at 0 °C resulted in the formation of epoxides **39** (or **40**) (40%), **40** (or **39**) (25%),[22] and **41** (18%), as well as **42** (or **43**) (22%), **43** (or **42**) (11%), and **44** (7%) along with some unidentified side products. The use of methyl(trifluoromethyl)dioxirane[21] (CH_3CN, ethylenediaminetetraacetic acid disodium salt [Na_2-(EDTA)], $NaHCO_3$, potassium peroxymonosulfate (Oxone), 0 °C] resulted in improved yields and regio- and stereoselectivities compared to *m*CPBA and dimethyldioxirane.[8,12,23] Thus, olefins **37** and **38** were converted to epoxides **39** (or **40**) (45%) and **40** (or **39**) (28%) and epoxides **42** (or **43**) (60%) and **43** (or **42**) (15%), respectively. No side-chain epoxidation was observed in either case. These results paved the way for the final drive toward epothilone A (**1**).

4. Total Synthesis of Epothilone A and Analogues

Encouraged by the results of the model studies described above, we proceeded to assemble epothilone A (**1**). Scheme 8 shows the initial stages of the construction beyond the key building blocks **6**–**8**. Thus, aldol condensation of **8**[20] (2.3 equiv of LDA) with aldehyde **7** afforded diastereomeric products **45** and **46** (ca. 3:2 ratio by ^1H NMR), which as a mixture were coupled with homoallylic alcohol **6**[20] in the presence of EDC and 4-DMAP to afford, after chromatographic purification, pure esters **4** (52% overall yield from **8**) and **43** (31% overall yield from **8**).

Scheme 9. Epoxidation of Epothilone Framework: Total Synthesis of Epothilone A (**1**) and Analogues **51**–**57**[a]



[a] (a) 0.1 equiv of $RuCl_2(=CHPh)(PCy_3)_2$, CH_2Cl_2, 25 °C, 20 h, **3** (46%), **48** (39%); (b) 20% CF_3COOH (TFA) in CH_2Cl_2, 0 °C, 3 h, **3** → **49** (90%); **48** → **50** (92%); (c) 0.8–1.2 equiv of *m*CPBA, $CHCl_3$, −20 → 0 °C, 12 h, **49** → **1** (35%); **51** (13%), **52** (or **53**) (9%), **53** (or **52** (7%), **54** (or **55**) (5%), **55** (or **54**) (5%); **1** → **54** (or **55**) (35%), **55** (or **54**) (33%), **57** (6%); (d) 1.3–2.0 equiv of *m*CPBA, $CHCl_3$, −20 → 0 °C, 12 h, **1** (15%), **51** (10%), **52** (or **53**) (10%), **53** (or **52**) (8%), **54** (or **55**) (8%), **55** (or **54**) (7%), **56** (5%), **57** (5%); (e) 1.0 equiv of dimethyldioxirane, CH_2Cl_2/acetone, 0 °C, **1** (50%), **51** (15%), **52** (or **53**) (5%), **53** (or **52**) (5%); (f) excess of CF_3COCH_3, 8.0 equiv of $NaHCO_3$, 5.0 equiv of Oxone, CH_3CN/Na_2EDTA (2:1), 0 °C, **1** (62%), **51** (13%).

The olefin metathesis reaction of **4** (6*R*,7*S* stereochemistry as proven by conversion to epothilone A) proceeded smoothly in the presence of the $RuCl_2(=CHPh)(PCy_3)_2$ catalyst, as shown in Scheme 9, to afford cyclic systems **3** ($J_{12,13}$ = 10.5 Hz) (46%) and **48** ($J_{12,13}$ = 15.0 Hz) (39%). The silyl ethers from **3** and

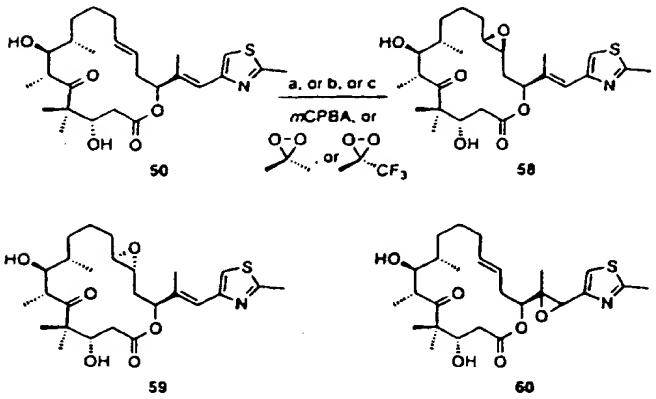
(20) Nicolaou, K. C.; Ninkovic, S.; Sarabia F.; Vourloumis, D.; He, Y.; Vallberg, H.; Finlay, M. R. V.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 7974–7991 (accompanying paper).

(21) Yang, D.; Wong, M.-K.; Yip, Y.-C. *J. Org. Chem.* **1995**, *60*, 3887–3889.

(22) Preliminary biological experiments indicated that compounds **39** and **40**, **52**–**55**, **64**, and **65**, **67**, and **68** did not induce significant tubulin polymerization, and therefore, the determination of their stereochemistry at the position of the epoxide was not pursued further: Nicolaou, K. C.; et al. Unpublished results.

(23) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847–2853.

Scheme 10. Synthesis of Epothilones **58**–**60**[a]



[a] Reagents and conditions: (a) 0.9–1.3 equiv of *m*CPBA, $CHCl_3$, −20 — 0 °C, 12 h, **58** (or **59**) (5%), **59** (or **58**) (5%), **60** (60%); (b) 1.0 equiv of dimethyldioxirane, CH_2Cl_2/acetone, 0 °C, **58** (or **59**) (10%), **59** (or **58**) (10%), **60** (40%); (c) excess of CF_3COCH_3, 8.0 equiv of $NaHCO_3$, 5.0 equiv of Oxone, MeCN/Na_2EDTA (2:1), 0 °C, **58** (or **59**) (45%), **59** (or **58**) (35%).

48 were removed by exposure to CF_3COOH in CH_2Cl_2, affording dihydroxy compounds **49** (90%) and **50** (92%), respectively.

The *cis*-olefin **49** was converted to epothilone A (**1**) by the action of *m*CPBA (0.8–1.2 equiv) in a reaction that, in addition to **1** (35%), produced the isomeric epoxides **51** (13%), **52** (or **53**) (9%), and **53** (or **52**) (7%),[22] as well as bis(epoxides) **54** (or **55**) and **55** (or **54**) (10% total yield).[22] Reaction of olefin **49** with excess *m*CPBA (1.3–2.0 equiv) resulted in a different product distribution: **1** (15%), **51** (10%), **52** (or **53**) (10%), **53** (or **52**) (8%), **54** (or **55**) (8%), **55** (or **54**) (7%), **56** (5%), and **57** (5%). The action of dimethyldioxirane[8,12,23] (CH_2Cl_2, 0 °C) on **49** gave mainly **1** (50%) and **51** (15%), together with small amounts of **53** (or **54**) and **54** (or **53**) (10% total yield). However, we found that the preferred procedure for this epoxidation was the one employing methyl(trifluoromethyl)-dioxirane,[21] a method that furnished epothilone A (**1**) in 62% yield, together with smaller amount of its α-epoxide epimer **51** (13% yield). Chromatographically purified synthetic epothilone A (**1**) exhibited properties identical to those of an authentic sample (TLC, HPLC, $[\alpha]_D$, IR, ^1H and ^{13}C NMR, and mass spectroscopy).[24] Further oxidation of pure epothilone A (**1**) with *m*CPBA (0.8–1.1 equiv) resulted in the formation of bis-(epoxides) **54** (or **55**) (35%) and **55** (or **54**) (32%) along with sulfoxide **57** (6%), confirming the C12–C13 stereochemical assignments shown in Scheme 9. Under similar conditions, α-isomeric epoxide **51** was recovered unreacted.

The *trans*-olefinic compound **50** gave rise to another series of epothilones A (**58**–**60**) as shown in Scheme 10. Thus, epoxidation of **50** with 1.0 equiv of *m*CPBA furnished compounds **58** (5%), **59** (5%), and **60** (60%, stereochemistry unassigned). Similarly, epoxidation of **50** with 1.0 equiv of dimethyldioxirane[8,12,23] resulted in the formation of **58** (10%), **59** (10%), and **60** (40%). Interestingly, however, the action of methyl(trifluoromethyl)dioxirane[21] led only to **58** (45%) and **59** (35%) in a much cleaner fashion.

The stereochemistry of **58** and **59** was tentatively assigned on the basis of ^1H–^1H NOESY and ^1H–^1H COSY experiments and computer modeling. Thus, molecular dynamics calculations revealed significant differences between the structures of the two epimeric epoxides with regard to the spacial arrangements

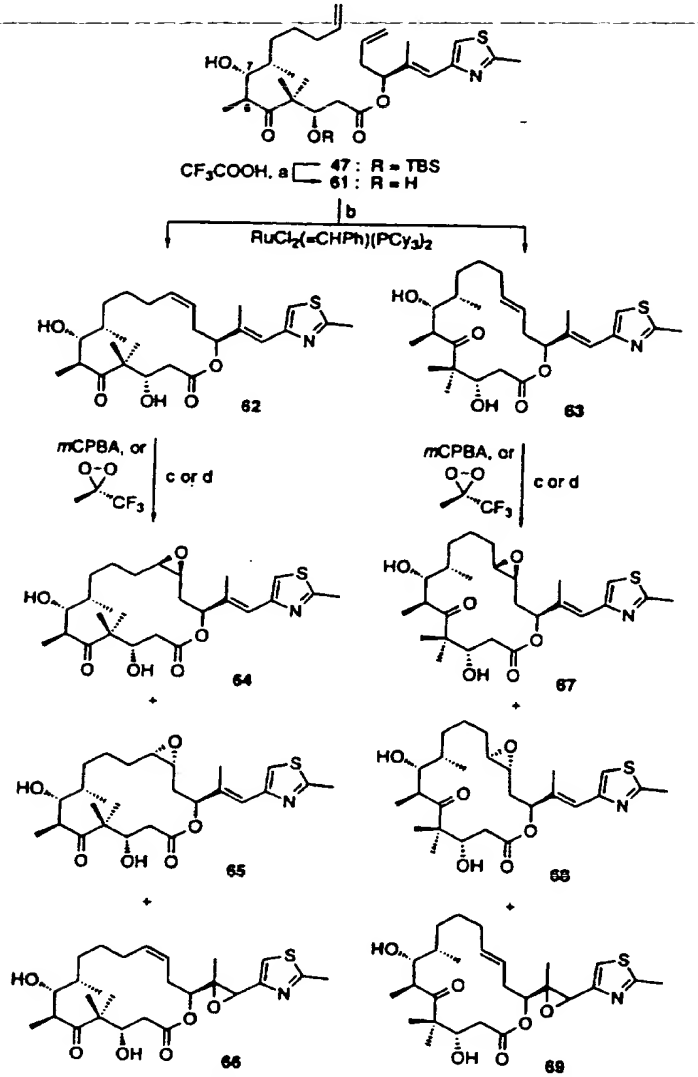
(24) We thank Dr. G. Höfle for a sample of natural epothilone A (**1**).

Figure 3. Computer-generated minimized structures of epothilones **58** (*trans*-12*S*,13*S*-epothilone A) and **59** (*trans*-12*R*,13*R*-epothilone A). ^1H–^1H NOESY derived NOE's between protons (intensity, distance): For **58**: H_{17}–H_3 (weak, 6.21 Å), H_{17}–H_8 (none, 8.13 Å), H_{17}–H_{12} (none, 4.18 Å), H_{17}–H_{13} (none, 5.30 Å). For **59**: H_{17}–H_3 (strong, 2.28 Å), H_{17}–H_6 (strong, 2.57 Å), H_{17}–H_{12} (weak, 3.78 Å), H_{17}–H_{13} (strong, 2.87 Å). The epothilone atoms are colored according to the following code: carbon, green; hydrogen, white; oxygen, red; nitrogen, blue; sulfur, yellow. Molecular dynamics and minimization calculations (CV Force Field) were performed on a SGI Indigo-2 workstation using Insight II (Biosym Technologies, Inc., San Diego, CA). Pictures were created using AVS (AVS Inc., Waltham, MA) and locally developed modules running on a DEC Alpha 3000/500 with a Kubota Pacific Denali graphics card.

of the side chain and the macrolactone. In the (12*S*,13*S*)-epoxide **58**, these two subunits assume remote spacial orientations, while in the (12*R*,13*R*)-epoxide **59**, the side chain and the large ring take up overlapping positions (see Figure 3). These calculated conformations were supported by the 2D NMR experiments showing, in the case of **59**, NOE's between H-17 and several of the macrocyclic protons (H_{17}–H_3, H_{17}–H_6, H_{17}–H_{12}, H_{17}–H_{13}), whereas similar experiments with **58** revealed NOE's between H_{17}–H_3 but not between H_{17}–H_6, H_{17}–H_{12}, and H_{17}–H_{13}.

To expand the epothilone A library, we utilized the 6*S*,7*R*-stereoisomer **61** (obtained from **47** by CF_3COOH-induced desilylation in 90% yield) in the olefin metathesis reaction to afford cyclic compounds **62** ($J_{12,13}$ = 9.8 Hz) (20%) and **63** ($J_{12,13}$ = 15.0 Hz) (69%) (Scheme 11). , Epoxidation of the dihydroxy macrocycle **62** with *m*CPBA (0.8–1.2 equiv) in $CHCl_3$ at −20 — 0 °C gave isomeric epoxides **64** (or **65**) (25%) and **65** (or **64**) (23%).[22] Side-chain epoxide **66** was not isolated in this case. Similarly, diol **63** furnished **67** (or **68**) (24%), **68** (or **67**) (19%),[22] and **69** (31%) under the same reaction conditions. Again, epoxidation of compounds **62** and **63** using methyl(trifluoromethyl)dioxirane[21] resulted in cleaner formation

Scheme 11. Synthesis of Epothilones **64**–**69**[a]



[a] (a) 20% CF_3COOH in CH_2Cl_2, 0 °C, 3 h, 90%; (b) 0.1 equiv of $RuCl_2(=CHPh)(PCy_3)_2$, CH_2Cl_2, 25 °C, 20 h, **62** (20%), **63** (69%); (c) 0.8–1.2 equiv of *m*CPBA, $CHCl_3$, −20 → 0 °C, 12 h, **62** → **64** (or **65**) (25%), **65** (or **64**) (23%); **63** → **67** (or **68**) (24%), **68** (or **67**) (19%), **69** (31%); (d) excess of CF_3COCH_3, 8.0 equiv of $NaHCO_3$, 5.0 equiv of Oxone, CH_3CN/Na_2EDTA (2:1), 0 °C, **62** → **64** (or **65**) (58%), **65** (or **64**) (29%); **63** → **67** (or **68**) (44%), **68** (or **67**) (21%).

of epoxides **64** (or **65**) (58%) and **65** (or **64**) (29%) and in epoxides **67** (or **68**) (44%) and **68** (or **67**) (21%), respectively.

5. Conclusion

In this article, we describe studies culminating in the total synthesis of epothilone A (**1**) and several of its analogues by an olefin metathesis approach, which was also the basis of independently initiated studies by Danishefsky,[9] Schinzer,[12] and Taylor.[7h] Not only did we explore the scope and limitations of this new reaction in total synthesis, but we also succeeded in the production of a series of epothilone A models and analogues for biological investigations and further chemical explorations. The high convergence and relative simplicity of the chemistry involved in this construction make this strategy amenable to combinatorial synthesis[25] for the generation of large libraries of these structures. This goal as well as improvements and modifications of the sequences described are currently being pursued in these laboratories.

Experimental Section

General Techniques. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF), toluene, and ethyl ether (ether) were distilled from sodium–benzophenone, and methylene chloride (CH_2Cl_2), from calcium hydride. Anhydrous solvents were also obtained by passing them through commercially available alumina column. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at highest commercial quality and used without further purification unless otherwise stated. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid or *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25, 0.50, or 1 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DMX-600 or AMX-500 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions with NBA as the matrix. Melting points (mp) are uncorrected and were recorded on a Thomas-Hoover Unimelt capillary melting point apparatus.

Sultam 14. Sodium-Mediated Alkylation of *N*-Acylsultam 13. A solution of sodium bis(trimethylsilyl)amide (NaHMDS, 236 mL, 1 M in THF, 1.05 equiv) was added over 30 min at −78 °C to a solution of *N*-acylsultam **13** (61.0 g, 0.225 mol) in THF (1.1 L, 0.2 M). After the resulting sodium enolate solution was stirred at −78 °C for 1 h, freshly distilled 5-iodo-1-pentene (58 mL, 0.45 mol, 2.0 equiv) in hexamethylphosphoramide (HMPA, 117 mL, 0.675 mol, 3.0 equiv) was added. The reaction mixture was allowed to slowly warm to 25 °C, quenched with water (1.5 L), and extracted with ether (3 × 500 mL). Drying ($MgSO_4$) and evaporation of the solvents gave crude sultam **14** (76.3 g), which was used without further purification. A pure sample of **14** was obtained by preparative thin-layer chromatography (250 μm silica gel plate, 10% EtOAc in hexanes): R_f = 0.57 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{22}_D$ −50.5 (*c* 2.00, $CHCl_3$); IR (film) ν_{max} 2939, 1694, 1331, 1216, 1131, 540 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.79–7.72 (m, 1 H, $CH_2CH{=}CH_2$), 5.00–4.90 (m, 2 H, $CH_2CH{=}CH_2$), 3.89 (dd, *J* = 7.5, 5.5 Hz, 1 H, CH_2CHN), 3.50 (d, *J* = 14.0 Hz, 1 H, CH_2SO_2), 3.43 (d, *J* = 14.0 Hz, 1 H, CH_2SO_2), 3.15–3.06 (m, 1 H, $(O{=}C)CH(CH_3)$), 2.10–2.00 (m, 3 H), 1.96–1.84 (m, 2 H), 1.78–1.68 (m, 1 H), 1.50–1.30 (m, 6 H), 1.16 (s, 3 H, $C(CH_3)_2$), 1.15 (d, *J* = 7.5 Hz, 3 H, $CHCH_3$), 0.97 (s, 3 H, $C(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 176.4, 138.2, 114.5, 65.1, 53.0, 48.1, 47.6, 44.5, 39.5, 38.5, 34.7, 33.2, 32.7, 26.3, 26.0, 20.7, 19.8, 16.5; HRMS (FAB) calcd for $C_{18}H_{30}NO_3S$ ($M + H^+$) 340.1946, found 340.1942.

Alcohol 15. Reductive Cleavage of Sultam 14. A solution of crude sultam **14** (76.0 g, 0.224 mol) in ether (200 mL) was added to a stirred suspension of lithium aluminum hydride (LAH, 9.84 g, 0.246 mol, 1.1 equiv) in ether (900 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 15 min, quenched by addition of water (9.8 mL), and warmed to 0 °C. Sequential addition of 15% aqueous sodium hydroxide solution (9.8 mL) and water (29.4 mL) was followed by warming the reaction mixture to 25 °C. After the mixture was stirred for 5 h, the aluminum salts were removed by filtration through Celite, the filtrate was dried ($MgSO_4$), and the solvent was removed by distillation under atmospheric pressure. Vacuum distillation (bp 85 °C at 8 mmHg) furnished pure alcohol **15** as a colorless oil (17.1 g, 60% from sultam **14**): R_f = 0.40 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{22}_D$ −11.1 (*c* 1.41, $CHCl_3$); IR (film) ν_{max} 3344, 2956, 2927, 2873, 1641, 1460, 1033, 910, 803 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.85–5.77 (m, 1 H,

(25) Nicolaou, K. C.; Winssinger, N.; Pastor, J. A.; Ninkovic, S.; Sarabia F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E. *Nature* **1997**, *387*, 268–272.

$CH_2CH{=}CH_2$), 5.03−4.93 (m, 2 H, $CH_2CH{=}CH_2$), 3.53−3.49 (dd, J = 10.5, 6.0 Hz, 1 H, CH_2OH), 3.44−3.41 (dd, J = 10.5, 6.5 Hz, 1 H, CH_2OH), 2.09−2.01 (m, 2 H), 1.67−1.58 (m, 1 H, $HOCH_2CH(CH_3)$) 1.51−1.34 (m, 3 H), 1.17−1.08 (m, 1 H) 0.92 (d, J = 6.5 Hz, 3 H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 138.8, 114.2, 68.0, 35.5, 33.9, 32.5, 26.2, 16.4.

Aldehyde 7. Oxidation of Alcohol 15. To a solution of alcohol **15** (0.768 g, 6.0 mmol) in CH_2Cl_2 (30 mL, 0.2 M) were added powdered 4 Å molecular sieves (1.54 g), 4-methylmorpholine *N*-oxide (NMO, 1.06 g, 9.0 mmol, 1.5 equiv), and tetrapropylammonium perruthenate (TPAP, 0.105 g, 0.3 mmol, 0.05 equiv) at room temperature. After the mixture was stirred for 30 min, the disappearance of starting material was indicated by TLC. Celite was added (1.54 g), and the suspension was filtered through silica gel and eluted with CH_2Cl_2. The solvent was carefully distilled off under atmospheric pressure to yield aldehyde **7** (0.721 g, 95%) as a colorless oil: R_f = 0.69 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{22}_D$ +18.3 (*c* 2.35, $CHCl_3$); IR (film) ν_{max} 2934, 1707, 1463, 1238, 912 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.58 (d, 1 H, CHO), 5.80−5.71 (m, 1 H, $CH_2CH{=}CH_2$), 5.00−4.90 (m, 2 H, CH_2-$CH{=}CH_2$), 2.36−2.27 (m, 1 H), 2.10−2.00 (m, 2 H), 1.73−1.65 (m, 1 H), 1.42−1.30 (m, 3 H), 1.06 (d, J = 7.0 Hz, 3 H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 204.9, 138.0, 114.7, 46.0, 33.5, 29.7, 26.0, 13.1.

Silyl Ether 17a. Silylation of Alcohol 16a. Alcohol **16a** (5.0 g, 0.068 mol) was dissolved in DMF (70 mL, 1.0 M), the solution was cooled to 0 °C, and imidazole (9.2 g, 0.135 mol, 2.0 equiv) was added. After the mixture was stirred for 10 min, *tert*-butylchlorodiphenylsilane (TPSCl, 24 mL, 0.088 mol, 1.3 equiv) was added and the reaction mixture was allowed to stir for 30 min at 0 °C and for 1 h at 25 °C. Ether (70 mL) was added, followed by saturated aqueous $NaHCO_3$ solution (70 mL). The organic phase was separated, and the aqueous layer was extracted with ether (50 mL) and washed with water (2 × 120 mL) and saturated aqueous NaCl solution (120 mL). The organic extract was dried ($MgSO_4$) and filtered through Celite, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 5% EtOAc in hexanes) provided silyl ether **17a** (18.9 g, 90%): R_f = 0.28 (5% EtOAc in hexanes); $[\alpha]^{22}_D$ −1.8 (*c* 1.14, $CHCl_3$); IR (film) ν_{max} 2957, 2930, 2857, 1471, 1427, 1111, 824, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72−7.67 (m, 4 H, $SiC(CH_3)_3(C_6H_5)_2$), 7.47−7.38 (m, 6 H, $SiC(CH_3)_3(C_6H_5)_2$), 3.86 (dd, J = 12.0, 3.0 Hz, 1 H, CH_2OTPS), 3.72 (dd, J = 12.0, 4.5 Hz, 1 H, CH_2OTPS), 3.16−3.12 (m, 1 H, CH_2−O(epoxide)CH, 2.76 (dd, J = 5.0, 4.0, 1 H, CH_2−O(epoxide)CH), 2.62 (dd, J = 5.0, 3.0, 1 H, CH_2−O(epoxide)CH), 1.08 (s, 9 H, $SiC(CH_3)_3(C_6H_5)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 135.5, 133.2, 129.7, 127.6, 64.2, 52.2, 44.3, 26.7, 19.1.

Silyl Ether 17b. Silylation of Alcohol 16b. By following the procedure described for the synthesis of silyl ether **17a**, alcohol **16b** (5.0 g, 0.068 mol) in DMF (70 mL, 1.0 M) was treated with imidazole (9.2 g, 0.135 mol, 2.0 equiv) and *tert*-butylchlorodiphenylsilane (24 mL, 0.088 mol, 1.3 equiv) to yield silyl ether **17b** (19.8 g, 94%).

Alcohol 18a. Opening of Epoxide 17a with Vinyl Cuprate. To a solution of tetravinyltin (3.02 mL, 16.6 mmol, 1.25 equiv) in THF (44 mL) was added *n*-butyllithium (41.5 mL, 1.6 M in hexanes, 5.0 equiv) at −78 °C, and the reaction mixture was stirred for 45 min. The resulting solution of vinyllithium was transferred via cannula to a solution of azeotropically dried (2 × 5 mL toluene) copper(I) cyanide (2.97 g, 33.2 mmol, 2.5 equiv) in THF (44 mL) at −78 °C, and the mixture was allowed to warm to −30 °C. Epoxide **17a** (4.14 g, 13.3 mmol) in THF (44 mL) was transferred via cannula to this vinyl cuprate solution, and the mixture was stirred at −30 °C for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (150 mL), filtered through Celite, extracted with ether (2 × 100 mL), and dried ($MgSO_4$). After removal of the solvents under reduced pressure, flash column chromatography (silica gel, 3% EtOAc in hexanes) furnished alcohol **18a** (5.01 g, 86%) as a pale yellow oil: R_f = 0.33 (silica gel, 10% EtOAc in hexanes); $[\alpha]^{22}_D$ −2.0 (*c* 2.20, $CHCl_3$); IR (film) ν_{max} 3071, 2930, 2858, 1428, 1111, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70−7.65 (m, 4 H, $SiC(CH_3)_3(C_6H_5)_2$), 7.47−7.38 (m, 6 H, $SiC(CH_3)_3(C_6H_5)_2$), 5.84−5.75 (m, 1 H, $CH_2CH{=}CH_2$), 5.11−5.04 (m, 2 H, $CH_2CH{=}CH_2$), 3.82−3.76 (m, 1 H, $CHOH$), 3.67 (dd, J = 10.5, 3.5 Hz, 1 H, CH_2OTPS), 3.56 (dd, J = 10.5, 7.0 Hz, 1 H, CH_2OTPS), 2.27−2.22 (m, 2 H, $CH_2CH{=}CH_2$), 2.17 (bs, 1 H, OH), 1.08 (s, 9 H, $SiC(CH_3)_3(C_6H_5)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 135.6, 135.4, 134.3, 134.3, 133.1, 129.9, 129.7, 127.8, 127.6, 117.4, 71.2, 67.3, 37.5, 26.8, 19.2; HRMS (FAB) calcd for $C_{21}H_{28}NaO_2Si$ (M + Na^+) 363.1756, found 363.1773.

Alcohol 18b. Opening of Epoxide 17b with Vinyl Cuprate. By following the procedure described for the synthesis of alcohol **18a**, epoxide **17b** (1.97 g, 6.3 mmol) yielded alcohol **18b** (1.78 g, 83%).

Keto Ester 20. Horner−Wadsworth−Emmons Reaction of Aldehyde 12 with Phosphonate 19. A solution of phosphonate **19** (23.6 g, 94 mmol, 1.2 equiv) in THF (100 mL) was transferred *via* cannula to a suspension of sodium hydride (60% dispersion in mineral oil, 5.0 g, 125 mmol, 1.6 equiv) in THF (200 mL) at 25 °C. After being stirred for 15 min, the reaction mixture was cooled to 0 °C, a solution of aldehyde **12** (10.0 g, 78 mmol) in THF (20 mL) was added via cannula, and the ice bath was removed. After 1 h at 25 °C, TLC indicated the disappearance of aldehyde **12**. The mixture was then separated between water (320 mL) and hexanes (100 mL). The aqueous layer was extracted with hexanes (100 mL), and the combined organic layers were successively washed with water (200 mL) and saturated aqueous NaCl solution (200 mL). Drying ($MgSO_4$), concentration under reduced pressure, and purification by flash column chromatography (silica gel, 10% EtOAc in hexanes) yielded keto ester **20** (17.4 g, 99%) as a yellow oil. R_f = 0.58 (silica gel, 20% EtOAc in hexanes); IR (film) ν_{max} 2977, 1714, 1645, 1318, 1297, 1158 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.91 (d, J = 15.5 Hz, 1 H, $CH{=}CHCOO$), 5.77 (d, J = 15.5 Hz, 1 H, $CH{=}CHCOO$), 2.47 (q, J = 7.0 Hz, 2 H, CH_2-CH_3), 1.47 (s, 9 H, $C(CH_3)_3$), 1.25 (s, 6 H, $C(CH_3)_2$), 0.99 (t, J = 7.0 Hz, 3 H, CH_2CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 211.7, 165.5, 150.3, 122.2, 80.5, 50.2, 31.2, 28.0, 23.5, 7.9; HRMS (FAB) calcd for $C_{13}H_{23}O_3$ (M + H^+) 227.1647, found 227.1656.

Keto Acid 21. Hydrolysis of Keto Ester 20. Keto ester **20** (17.4 g, 77 mmol) in CH_2Cl_2 (39 mL, 2 M) was treated with trifluoroacetic acid (TFA, 39 mL, 2 M) at 25 °C. Within 30 min TLC indicated disappearance of the ester. The mixture was concentrated under reduced pressure, dissolved in saturated aqueous $NaHCO_3$ solution (20 mL), and washed with ether (2 × 20 mL). The aqueous phase was then acidified to pH ~ 2 with 4 N HCl, saturated with NaCl, and extracted with EtOAc (6 × 20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give pure keto acid **21** (13.0 g, 99%) as a clear oil, which solidified on standing: R_f = 0.20 (silica gel, 2% TFA in CH_2Cl_2); mp 56−57 °C (EtOAc); IR (film) ν_{max} 2979, 1712, 1647, 1300, 1201 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, J = 16.0 Hz, 1 H, $CH{=}CHCOOH$), 5.89 (d, J = 16.0 Hz, 1 H, $CH{=}CHCOOH$), 2.50 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 1.31 (s, 6 H, $C(CH_3)_2$), 1.03 (t, J = 7.0 Hz, 3 H, CH_2CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 211.8, 171.3, 154.3, 119.6, 50.4, 31.2, 23.2, 7.7; HRMS (FAB) calcd for $C_9H_{14}NaO_3$ (M + Na^+) 193.0841, found 193.0846.

Keto Ester 22a. EDC Coupling of Alcohol 18a with Keto Acid 21. A solution of keto acid **21** (2.43 g, 14.3 mmol, 1.2 equiv), 4-(dimethylamino)pyridine (4-DMAP, 0.145 g, 1.2 mmol, 0.1 equiv), and alcohol **18a** (4.048 g, 11.9 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL, 0.3 M) was cooled to 0 °C and then treated with 1-ethyl-3-((dimethylamino)propyl)carbodiimide hydrochloride (EDC, 2.74 g, 14.3 mmol, 1.2 equiv). The reaction mixture was stirred at 0 °C for 2 h and then at 25 °C for 12 h. The solution was concentrated to dryness in vacuo, and the residue was taken up in EtOAc (10 mL) and water (10 mL). The organic layer was separated, washed with saturated NH_4Cl solution (10 mL) and water (10 mL), and dried ($MgSO_4$). Evaporation of the solvents followed by flash column chromatography (silica gel, 4% EtOAc in hexanes) resulted in pure keto ester **22a** (5.037 g, 86%): R_f = 0.41 (silica gel, 10% EtOAc in hexanes); $[\alpha]^{22}_D$ −6.1 (*c* 1.22, $CHCl_3$); IR (film) ν_{max} 3072, 2960, 2933, 2858, 1715, 1645, 1470, 1428, 1295, 1181, 1112, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66−7.64 (m, 4 H, $SiC(CH_3)_3(C_6H_5)_2$), 7.44−7.36 (m, 6 H, $SiC(CH_3)_3(C_6H_5)_2$), 7.05 (d, 1 H, J =16.0 Hz, $CH{=}CHCOO$), 5.86 (d, J =16.0 Hz, 1 H, $CH{=}CHCOO$), 5.79−5.70 (m, 1 H, $CH_2CH{=}CH_2$), 5.15−5.04 (m, 3 H, $CH_2CH{=}CH_2$ and CO_2CH), 3.76−3.70 (m, 2 H, CH_2OTPS), 2.53−2.36 (m, 4 H), 1.29 (s, 6 H, $C(CH_3)_2$), 1.04 (s, 9 H, $SiC(CH_3)_3(C_6H_5)_2$), 1.01 (t, J = 7.0 Hz, 3 H, $CH_3CH_2C{=}O$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 211.4, 165.7, 151.7, 135.5, 135.4, 133.2, 129.6, 127.6, 120.6, 117.9, 73.6, 64.3, 50.4, 35.0, 31.3, 26.6, 23.6, 23.5, 19.2, 7.9; HRMS (FAB) calcd for $C_{30}H_{40}CsO_4Si$ (M + Cs^+) 625.1750, found 625.1765.

Trienes 23 and 24. Aldol Condensation of Ester 22a with Aldehyde 7. A solution of keto ester **22a** (1.79 g, 3.63 mmol, 1.0 equiv) in THF (15 mL) was added via cannula to a freshly prepared solution of lithium diisopropylamide [LDA; formed by addition of *n*-BuLi (2.83 mL, 1.6 M solution in hexanes, 4.58 mmol, 1.25 equiv) to a solution of diisopropylamine (0.61 mL, 4.36 mmol, 1.2 equiv) in THF (30 mL) at −10 °C and stirring for 30 min] at −78 °C. After 15 min, the reaction mixture was allowed to warm to −40 °C and was stirred for 45 min. The reaction mixture was cooled to −78 °C, and a solution of aldehyde **7** (0.740 g, 5.8 mmol, 1.6 equiv) in THF (15 mL) was added dropwise. The resulting mixture was stirred for 15 min, then warmed to −40 °C for 30 min, cooled back to −78 °C, and then quenched by slow addition of saturated aqueous NH_4Cl solution (10 mL). The reaction mixture was warmed to 25 °C and diluted with EtOAc (10 mL), and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure, and subjected to flash chromatographic purification (silica gel, 5 → 20% EtOAc in hexanes) to afford a mixture of aldol products **23** (926 mg, 42%) and **24** (724 mg, 33%), along with unreacted starting keto ester **22a** (178 mg, 10%). **23**: R_f = 0.40 (silica gel, 18% EtOAc in hexanes); $[\alpha]^{22}_D$ −11.4 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3518, 2962, 2932, 2858, 1722, 1644, 1294, 1182, 1114, 989, 702 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.67−7.63 (m, 4 H, $SiC(CH_3)_3(C_6H_5)_2$), 7.45−7.40 (m, 2 H, $SiC(CH_3)_3(C_6H_5)_{22}$), 7.40−7.35 (m, 4 H, $SiC(CH_3)_3(C_6H_5)_2$), 7.03 (d, 1 H, J =15.8 Hz, CH=CHCOO), 5.92 (d, J = 15.8 Hz, 1 H, CH=CHCOO), 5.84−5.76 (m, 1 H, CH_2CH=CH_2), 5.76−5.68 (m, 1 H, CH_2CH=CH_2), 5.14−5.09 (m, 1 H, CO_2CH), 5.08 (d, J = 17.2 Hz, 1 H, CH_2CH=CH_2), 5.04 (d, J =10.1 Hz, 1 H, CH_2CH=CH_2), 4.99 (d, J =18.9 Hz, 1 H, CH_2CH=CH_2), 4.92 (d, J = 10.2 Hz, 1 H, CH_2CH=CH_2), 3.76−3.69 (m, 2 H, CH_2OTPS), 3.29 (d, J = 8.9 Hz, 1 H, CHOH(CHCH$_3$)), 3.16 (s, 1 H, CHOH(CHCH$_3$)), 3.13 (qd, J =7.0, 1.8 Hz, 1 H, CH_3CH(C=O)), 2.52−2.45 (m, 1 H), 2.42−2.35 (m, 1 H), 2.09−1.97 (m, 2 H), 1.76−1.68 (m, 1 H), 1.52−1.43 (m, 2 H), 1.30 (s, 3 H, $C(CH_3)_2$), 1.30 (s, 3 H, $C(CH_3)_2$), 1.30−1.25 (m, 1 H), 1.12−1.00 (m, 1 H), 1.03 (s, 9 H, $SiC(CH_3)_3(C_6H_5)_2$), 1.01 (d, J = 7.1 Hz, 3 H, CH_3CH(C=O), 0.77 (d, J = 6.8 Hz, 3 H, CH_3CHCH_2; ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 217.0, 165.2, 150.1, 138.9, 135.4, 135.4, 135.4, 133.1, 133.1, 129.6, 129.6, 127.6, 127.5, 121.5, 117.9, 114.2, 74.9, 73.8, 64.4, 51.6, 41.5, 35.5, 35.2, 34.3, 32.2, 26.8, 26.2, 23.3, 23.3, 19.4, 15.6, 10.4; HRMS (FAB) calcd for $C_{38}H_{54}CsO_5Si$ (M + Cs^+) 751.2795, found 751.2766. **24**: R_f = 0.30 (silica gel, 18% EtOAc in hexanes); $[\alpha]^{22}_D$ −1.33 (*c* 0.60, $CHCl_3$); IR (film) ν_{max} 3521, 2962, 2932, 2858, 1722, 1644, 1294, 1182, 1113, 988, 702 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.68−7.63 (m, 4 H, $SiPh_2$), 7.45−7.40 (m, 2 H, $SiC(CH_3)_3(C_6H_5)_2$), 7.40−7.35 (m, 4 H, $SiC(CH_3)_3(C_6H_5)_2$), 7.03 (d, 1 H, J = 15.8 Hz, CH=CHCOO), 5.90 (d, J = 15.8 Hz, 1 H, CH=CHCOO), 5.82−5.68 (m, 2 H, 2 × CH_2CH=CH_2), 5.14−5.08 (m, 1 H, CO_2CH), 5.09 (d, J = 16.9 Hz, 1 H, CH_2CH=CH_2), 5.05 (d, J = 10.1 Hz, 1 H, CH_2CH=CH_2), 4.99 (d, J = 17.1 Hz, 1 H, CH_2CH=CH_2), 4.95 (d, J = 10.1 Hz, 1 H, CH_2-CH=CH_2), 3.76−3.69 (m, 2 H, CH_2OTPS), 3.44 (dd, J = 6.6, 3.9 Hz, 1 H, CHOH(CHCH$_3$)), 3.13−3.08 (m, 1 H, CH_3CH(C=O)), 2.69 (bs, 1 H, CHOH(CHCH$_3$)), 2.53−2.47 (m, 1 H), 2.43−2.37 (m, 1 H), 2.07−1.95 (m, 2 H), 1.48−1.25 (m, 5 H), 1.31 (s, 3 H, $C(CH_3)_2$), 1.29 (s, 3 H, $C(CH_3)_2$), 1.05 (d, J = 7.0 Hz, 3 H, CH_3CH(C=O)), 1.03 (s, 9 H, $SiC(CH_3)_3(C_6H_5)_2$), 0.92 (d, J = 6.6 Hz, 3 H, CH_3CHCH_2); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 216.1, 165.2, 150.3, 138.5, 135.5, 135.4, 135.4, 133.1, 133.1, 129.6, 129.6, 127.6, 127.6, 121.4, 117.9, 114.6, 75.1, 73.8, 64.4, 51.5, 42.6, 35.5, 35.1, 33.9, 32.6, 26.8, 26.0, 23.6, 23.3, 19.4, 15.0, 12.3; HRMS (FAB), calcd for $C_{38}H_{54}CsO_5Si$ (M + Cs^+) 751.2795, found 751.2771.

Hydroxy Lactone 25. Olefin Metathesis of Diene 23. To a solution of diene **23** (0.186 g, 0.3 mmol) in CH_2Cl_2 (100 mL, 0.003 M) was added bis(tricyclohexylphosphine)benzylideneruthenium dichloride ($RuCl_2$(=CHPh)$(PCy_3)_2$, 25 mg, 0.03 mol, 0.1 equiv), and the reaction mixture was allowed to stir at 25 °C for 12 h. After the completion of the reaction was established by TLC, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (silica gel, 30% EtOAc in hexanes) to give *trans*-hydroxy lactone **25** (151 mg, 85%): R_f = 0.50 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{22}_D$ +65.9 (*c* 0.80, $CHCl_3$); IR (film) ν_{max} 3520, 2960, 2932, 2858, 1711, 1705, 1646, 1292, 1183, 1114, 982, 702, 505 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69−7.64 (m, 4 H, $SiC(CH_3)_3(C_6H_5)_2$), 7.46−7.36 (m, 6 H, $SiC(CH_3)_3(C_6H_5)_2$), 6.78 (d, J = 15.5 Hz, 1 H, CH=CHCOO), 5.98 (d, J = 15.5 Hz, 1 H, CH=CHCOO), 5.40 (ddd, J = 15.5, 8.5, 4.0 Hz, 1 H, CH=$CHCH_2$), 5.38 (ddd, J = 15.5, 8.5, 4.5 Hz, 1 H, CH=$CHCH_2$), 5.22−5.16 (m, 1 H, CO_2CH), 3.75 (dd, J = 10.5, 6.0 Hz, 1 H, CH_2OTPS), 3.58 (bs, 1 H, CHOH(CHCH$_3$)), 3.05 (qd, J = 6.5, 5.5 Hz, 1 H, CH_3CH(C=O)), 2.42 (d, J = 14.0 Hz, 1 H), 2.24−2.16 (m, 2 H), 2.12−2.04 (m, 1 H), 2.03−1.94 (m, 1 H), 1.55−1.40 (m, 2 H), 1.37 (s, 3 H, $C(CH_3)_2$), 1.28−1.04 (m, 3 H), 1.20 (s, 3 H, $C(CH_3)_2$), 1.15 (d, J = 7.0 Hz, 3 H, CH_3CH(C=O)), 1.05 (s, 9 H, $SiC(CH_3)_3(C_6H_5)_2$), 0.93 (d, J = 7.0 Hz, 3 H, CH_3CHCH_2); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 214.8, 164.9, 149.6, 135.5, 135.4, 133.2, 133.2, 132.7, 129.6, 129.6, 127.6, 127.6, 126.3, 122.5, 75.7, 73.2, 65.6, 52.2, 42.1, 38.2, 34.8, 33.2, 30.3, 27.2, 26.9, 23.4, 23.2, 19.4, 16.3, 14.6; HRMS (FAB) calcd for $C_{36}H_{50}O_5CsSi$ (M + Cs^+) 723.2482, found 723.2508.

Hydroxy Lactone 26. Olefin Metathesis of Diene 24. By following the procedure described above for the synthesis of hydroxy lactone **25**, a solution of diene **24** (0.197 g, 0.32 mmol) in CH_2Cl_2 (100 mL, 0.003 M) was treated with bis(tricyclohexylphosphine)-benzylideneruthenium dichloride ($RuCl_2$(=CHPh)$(PCy_3)_2$, 26 mg, 0.032 mol, 0.1 equiv) to produce, after flash chromatography (silica gel, 18 → 25% EtOAc in hexanes), *trans*-hydroxy lactone **26** (150 mg, 79%): R_f = 0.3 (silica gel, 18% EtOAc in hexanes); $[\alpha]^{22}_D$ −3.00 (*c* = 0.40, $CHCl_3$); IR (film) ν_{max} 3522, 2961, 2931, 2857, 1718, 1698, 1646, 1294, 1182, 1113, 702 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.67−7.63 (m, 4 H, $SiC(CH_3)_3(C_6H_5)_2$), 7.45−7.41 (m, 2 H, $SiC(CH_3)_3(C_6H_5)_2$), 7.40−7.36 (m, 4 H, $SiC(CH_3)_3(C_6H_5)_2$), 7.07 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.86 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.30 (ddd, J = 15.2, 7.4, 4.2 Hz, 1 H, CH=$CHCH_2$), 5.28 (ddd, J = 15.2, 7.5, 4.2 Hz, 1 H, CH=$CHCH_2$), 5.26−5.21 (m, 1 H, CO_2CH), 3.77 (dd, J = 10.7, 6.3 Hz, 1 H, CH_2OTPS), 3.70 (dd, 1 H, J = 10.7, 5.2 Hz, CH_2OTPS), 3.27 (d, J = 9.0, 1 H, CHOH(CHCH$_3$)), 3.13 (q, J = 6.9 Hz, 1 H, CH_3CH(C=O)), 2.87 (bs, 1 H, CHOH(CHCH$_3$)), 2.52−2.45 (m, 1 H), 2.34−2.26 (m, 1 H), 2.15−2.08 (m, 1 H), 1.97−1.89 (m, 1 H), 1.52−1.44 (m, 1 H), 1.40−1.31 (m, 1 H), 1.31 (s, 3 H, $C(CH_3)_2$), 1.30−1.20 (m, 1 H), 1.24 (s, 3 H, $C(CH_3)_2$), 1.12−1.00 (m, 1 H), 1.04 (s, 9 H, $SiC(CH_3)_3(C_6H_5)_2$), 1.01 (d, 3 H, J = 6.9 Hz, CH_3-CH(C=O)), 0.96 (d, 3 H, J = 6.6 Hz, CH_3CHCH_2), 0.93 (m, 1 H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 217.8, 165.3, 151.1, 135.5, 135.4, 133.3, 133.2, 133.1, 129.6, 129.6, 127.6, 127.6, 125.6, 121.5, 75.0, 73.4, 64.9, 51.0, 43.6, 35.6, 34.2, 32.7, 32.0, 26.9, 25.6, 25.2, 24.0, 19.4, 16.0, 7.0; HRMS (FAB) calcd for $C_{36}H_{50}O_5CsSi$ (M + Cs^+) 723.2482, found 723.2506.

Diol 27. Desilylation of TPS Ether 25. A solution of TPS ether **25** (145 mg, 0.23 mmol) in THF (4.7 mL, 0.05 M) was treated with glacial acetic acid (70 μL, 1.15 mmol, 5.0 equiv) and tetrabutylammonium fluoride (TBAF, 490 μL, 1 M solution in THF, 0.46 mmol, 2.0 equiv) at 25 °C. After the mixture was stirred for 36 h, no starting material was detected by TLC and the reaction mixture was quenched by addition of saturated aqueous NH_4Cl (10 mL). Extractions with ether (3 × 10 mL), drying ($MgSO_4$), and concentration was followed by flash chromatographic purification (silica gel, 50% EtOAc in hexanes) to provide diol **27** (78 mg, 92%): R_f = 0.30 (silica gel, ether), $[\alpha]^{22}_D$ +144.5 (*c* 0.51, $CHCl_3$); IR (film) ν_{max} 3440, 2933, 1706, 1646, 1293, 1183, 982 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.82 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 6.08 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.42 (ddd, J = 15.5, 8.0, 4.5 Hz, 1 H, CH=$CHCH_2$), 5.40 (ddd, J = 15.5, 8.5, 4.5 Hz, 1 H, CH=$CHCH_2$), 5.20−5.14 (m, 1 H, CO_2CH), 3.76 (dd, J = 12.0, 4.0 Hz, 1 H, CH_2OH), 3.72 (dd, J = 12.0, 6.5 Hz, 1 H, CH_2OH), 3.58 (dd, J = 5.0, 2.5 Hz, 1 H, CHOH(CHCH$_3$)), 3.06 (qd, J = 7.0, 6.0 Hz, 1 H, CH_3CH(C=O)), 2.38−2.34 (m, 1 H), 2.28−2.20 (m, 1 H), 2.12−2.03 (m, 1 H), 2.03−1.95 (m, 1 H), 1.55−1.42 (m, 2 H), 1.40 (s, 3 H, $C(CH_3)_2$), 1.22−1.08 (m, 2 H), 1.22 (s, 3 H, $C(CH_3)_2$), 1.15 (d, J = 7.0 Hz, 3 H, CH_3CH(C=O)), 1.08−0.86 (m, 1 H), 0.94 (d, J = 7.0 Hz, 3 H, CH_3CHCH_2); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 214.8, 165.3, 150.4, 133.0, 126.0, 122.1, 75.5, 73.7, 64.9, 52.1, 41.9, 38.0, 34.4, 33.0, 30.1, 26.9, 23.2, 22.7, 16.1, 14.6; HRMS (FAB), calcd for $C_{20}H_{33}O_4$ (M + H^+) 353.2328, found 353.2319.

Diol 28. Desilylation of TPS Ether 26. In accordance with the procedure describing the desilylation of TPS ether **25**, a solution of

TPS ether **26** (31 mg, 0.05 mmol) in THF (1.0 mL, 0.05 M) was treated with glacial acetic acid (15 μL, 0.25 mmol, 5.0 equiv) and tetrabutylammonium fluoride (TBAF, 105 μL, 1 M solution in THF, 0.10 mmol, 2.0 equiv) to yield diol **28** (17 mg, 95%) as a crystalline solid: R_f = 0.15 (silica gel, 50% EtOAc in hexanes); mp 128−129 °C (EtOAc−hexanes); $[\alpha]^{22}_D$ +45.6 (*c* 0.80, $CHCl_3$); IR (film) ν_{max} 3442, 2932, 1702, 1647, 1296, 1184, 974 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.14 (d, *J* = 16.0 Hz, 1 H, C*H*=CHCOO), 5.94 (d, *J* = 16.0 Hz, 1 H, CH=C*H*COO), 5.34 (ddd, *J* = 15.4, 7.6, 4.2 Hz, 1 H, C*H*=CHCH$_2$), 5.32 (ddd, *J* = 15.4, 7.6, 4.2 Hz, 1 H, C*H*=CHCH$_2$), 5.20−5.16 (m, 1 H, CO_2CH), 3.75−3.73 (m, 2 H, CH_2OH), 3.28 (dd, *J* = 9.0, 1.2 Hz, 1 H, C*H*OH(CHCH$_3$)), 3.13 (qd, *J* = 7.0, 1.2 Hz, 1 H, CH$_3$C*H*(C=O)), 2.81 (bs, 1 H, CHO*H*(CHCH$_3$)), 2.46−2.42 (m, 1 H), 2.36−2.30 (m, 1 H), 2.17−2.13 (m, 1 H), 1.97−1.92 (m, 1 H), 1.86 (bs, 1 H, CH$_2$O*H*), 1.51−1.46 (m, 1 H), 1.40−1.22 (m, 2H), 1.33 (s, 3 H, C(CH$_3$)$_2$), 1.27 (s, 3 H, C(CH$_3$)$_2$), 1.12−0.89 (m, 2 H) 1.01 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$-CH(C=O)), 0.96 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$CHCH$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 217.4, 165.8, 151.9, 133.6, 125.3, 121.2, 75.0, 74.4, 64.7, 51.0, 43.8, 35.6, 34.3, 32.7, 32.0, 25.5, 25.3, 24.0, 16.0, 9.9; HRMS (FAB) calcd for $C_{20}H_{33}O_5$ (M + H$^+$) 353.2328, found 353.2323.

Ester 22b. DCC Coupling of Alcohol 18b with Keto Acid 21. To a solution of alcohol **18b** (1.000 g, 2.94 mmol, 1.0 equiv), 1,3-dicyclohexylcarbodiimide (DCC, 0.836 g, 4.06 mmol, 1.4 equiv), and 4-dimethylaminopyridine (4-DMAP, 0.496 g, 4.06 mmol, 1.4 equiv) in toluene (30 mL, 0.1 M) was added keto acid **21** (0.638 g, 3.75 mmol, 1.2 equiv) at 25 °C. After 12 h the reaction was complete, as indicated by TLC. The reaction mixture was then passed through a short plug of silica gel, eluted with toluene, and concentrated under reduced pressure. The crude material was submitted to flash column chromatography (silica gel, 5% EtOAc in hexanes) to yield pure **22b** (1.38 g, 95%).

Dienes 29 and 30. Aldol Condensation of Ester 22b with Aldehyde 7. In accordance with the procedure described for the preparation of dienes **23** and **24**, keto ester **22b** (0.702 g, 1.43 mmol, 1.0 equiv) in THF (8.0 mL) was treated with lithium diisopropylamide [LDA; freshly prepared from *n*-butyllithium (1.12 mL, 1.6 M solution in hexanes, 1.79 mmol, 1.25 equiv) and diisopropylamine (241 μL, 1.72 mmol, 1.2 equiv) in THF (16 mL)] and aldehyde **7** (289 mg, 2.29 mmol, 1.6 equiv) in THF (3.0 mL) to afford a mixture of aldol products **29** (0.478 g, 54%) and **30** (0.210 g, 24%) along with unreacted starting material **22b** (79 mg, 11%).

Hydroxy Lactone 31. Olefin Metathesis of Diene 29. A solution of diene **29** (104 mg, 0.17 mmol) in CH_2Cl_2 (25 mL, 0.007 M) was treated with bis(tricyclohexylphosphine)benzylideneruthenium dichloride ((RuCl$_2$(=CHPh)(PCy$_3$)$_2$, 14 mg, 0.017 mmol, 0.1 equiv), in accordance with the procedure described for the preparation of hydroxy lactone **25**, to furnish, after flash column chromatography (silica gel, 5 → 17% EtOAc in hexanes), hydroxy lactone **31** (79 mg, 80%).

Hydroxy Lactone 32. Olefin Metathesis of Diene 30. A solution of diene **30** (20 mg, 0.03 mmol) in CH_2Cl_2 (10 mL, 0.003 M) was treated with bis(tricyclohexylphosphine)benzylideneruthenium dichloride (RuCl$_2$(=CHPh)(PCy$_3$)$_2$, 2.5 mg, 0.003 mmol, 0.1 equiv), in accordance with the procedure described for the preparation of hydroxy lactone **25**, to produce after preparative thin-layer chromatography (250 μm silica gel plate, 10% EtOAc in hexanes) hydroxy lactone **32** (15 mg, 81%).

Hydroxy Acids 33 and 34. Aldol Condensation of Acid 21 with Aldehyde 7. A solution of keto acid **21** (752 mg, 4.42 mmol, 1.0 equiv) in THF (22 mL) was added dropwise at −78 °C to a freshly prepared solution of LDA [formed by addition of *n*-BuLi (6.49 mL, 1.6 M solution in hexanes, 10.4 mmol, 2.35 equiv) to a solution of diisopropylamine (1.43 mL, 10.2 mmol, 2.3 equiv) in THF (44 mL) at −10 °C and stirring for 30 min]. After being stirred for 15 min, the reaction mixture was allowed to warm to −30 °C and stirred at that temperature for 1.5 h. The reaction mixture was cooled back to −78 °C and a solution of aldehyde **7** (0.891 g, 7.07 mmol, 1.6 equiv) in THF (22 mL) was added via cannula. The resulting mixture was stirred for 15 min at −78 °C, then warmed to −40 °C, stirred for 1 h, cooled to −78 °C, and quenched by slow addition of saturated aqueous NH_4Cl (10 mL) solution. The reaction mixture was warmed to 0 °C, and acetic acid (1.26 mL, 22.1 mmol, 5.0 equiv) was added, followed by warming to 25 °C. Extractions with EtOAc (6 × 15 mL), filtration through a short plug of silica gel, and concentration afforded, in high yield, a mixture of aldol products **33** and **34** along with unreacted starting acid **21** in a 35:50:15 ratio (^1H NMR). This crude material was used without further purification: ^1H NMR (500 MHz, $CDCl_3$; only signals for **33** and **34** are reported) δ 7.16 (d, *J* = 16.0 Hz, 1 H, C*H*=CHCOOH), 5.95 (d, *J* = 16.0 Hz, 1 H, CH=C*H*COOH), 5.86−5.73 (m, 1 H, CH$_2$C*H*=CH$_2$), 5.02−4.91 (m, 2 H, CH$_2$CH=C*H*$_2$), 3.46−3.32 (m, 1 H, C*H*OH(CHCH$_3$)), 3.17−3.11 (m, 1 H, CH$_3$C*H*(C=O)), 2.09−1.98 (m, 2 H, C*H*$_2$CH=CH$_2$), 1.72−1.24 (m, 9 H), 1.14−1.02 (m, 5 H), 0.95−0.81 (m, 3 H); HRMS (FAB) calcd for $C_{17}H_{29}O_4$ (M + H$^+$) 297.2066, found 297.2074.

Esters 35 and 36. EDC Coupling of Alcohol 6 with Keto Acids 33 and 34. By analogy to the procedure described above for the synthesis of ester **22a**, a solution of keto acids **33** and **34** (1.034 g crude), 4-(dimethylamino)pyridine (4-DMAP, 43 mg, 0.35 mmol), and alcohol **6** (1.1 g, 5.24 mmol) in CH_2Cl_2 (4 mL) was treated with 1-ethyl-3-((dimethylamino)propyl)carbodiimide hydrochloride (EDC, 1.00 g, 5.24 mmol) to provide, after column chromatography (silica gel, 20% EtOAc in hexanes), ester **35** (0.567 g, 29% from keto acid **21**) and ester **36** (0.863 g, 44% from keto acid **21**). **35**: R_f = 0.27 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{22}_D$ −7.3 (*c* 2.90, $CHCl_3$); IR (film) ν_{max} 3510, 2973, 2932, 1719, 1703, 1641, 1459, 1293, 1179, 985 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.03 (d, *J* = 16.0 Hz, 1 H, C*H*=CHCOO), 6.95 (s, 1 H, ArH), 6.53 (s, 1 H, ArC*H*=CCH$_3$), 5.95 (d, *J* = 16.0 Hz, 1 H, CH=C*H*COO), 5.80−5.69 (m, 2 H, 2 x CH$_2$C*H*=CH$_2$), 5.39 (t, *J* = 6.5 Hz, 1 H, CO_2CH), 5.10 (d, *J* = 17.5 Hz, 1 H, CH$_2$CH=C*H*$_2$), 5.05 (d, *J* = 10.5 Hz, 1 H, CH$_2$CH=C*H*$_2$), 4.97 (d, *J* = 17.0 Hz, 1 H, CH$_2$CH=C*H*$_2$), 4.93 (d, *J* = 10.0 Hz, 1 H, CH$_2$CH=C*H*$_2$), 3.43 (dd, *J* = 6.5, 4.0 Hz, 1 H, C*H*OH(CHCH$_3$)), 3.11 (qd, *J* = 7.0, 4.0 Hz, 1 H, CH$_3$C*H*(C=O)), 2.76 (bs, 1 H, C*H*OH(CHCH$_3$)), 2.69 (s, 3 H, CH$_3$-Ar), 2.57−2.47 (m, 2 H, C*H*$_2$CH=CH$_2$), 2.08 (d, *J* = 1.0 Hz, 3 H, ArCH=CC*H*$_3$), 2.07−1.93 (m, 2 H, C*H*$_2$CH=CH$_2$), 1.47−1.28 (m, 4 H), 1.30 (s, 3 H, C(CH$_3$)$_2$), 1.28 (s, 3 H, C(CH$_3$)$_2$), 1.05 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$CH(C=O)), 1.05−0.98 (m, 1 H), 0.91 (d, *J* = 6.5 Hz, 3 H, C*H*$_3$CHCH$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 216.3, 165.0, 164.7, 152.2, 150.5, 138.6, 136.9, 133.2, 121.4, 120.8, 117.8, 116.4, 114.6, 78.4, 75.0, 51.5, 42.6, 37.5, 35.3, 33.7, 32.5, 25.9, 23.2, 23.2, 19.1, 14.8, 12.2; HRMS (FAB) calcd for $C_{28}H_{42}NO_4S$ (M + H$^+$) 488.2835, found 488.2843. **36**: R_f = 0.34 (silica gel, 20% EtOAc in hexanes); $[\alpha]^{22}_D$ −9.2 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3519, 2930, 1716, 1641, 1457, 1293, 1179, 986 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, *J* = 16.0 Hz, 1 H, C*H*=CHCOO), 6.95 (s, 1 H, ArH), 6.54 (s, 1 H, ArC*H*=CCH$_3$), 5.96 (d, *J* = 15.5 Hz, 1 H, CH=C*H*COO), 5.84−5.69 (m, 2 H, 2 x CH$_2$C*H*=CH$_2$), 5.40 (t, *J* = 6.5 Hz, 1 H, CO_2CH), 5.10 (d, *J* = 17.0 Hz, 1 H, CH$_2$CH=C*H*$_2$), 5.05 (d, *J* = 10.5 Hz, 1 H, CH$_2$-CH=C*H*$_2$), 4.98 (d, *J* = 17.5 Hz, 1 H, CH$_2$CH=C*H*$_2$), 4.92 (d, *J* = 9.0 Hz, 1 H, CH$_2$CH=C*H*$_2$), 3.30 (dd, *J* = 8.5, 1.5 Hz, 1 H, C*H*OH-(CHCH$_3$)), 3.13 (qd, *J* = 7.0, 2.0 Hz, 1 H, CH$_3$C*H*(C=O)), 2.70 (s, 3 H, CH$_3$Ar), 2.57−2.49 (m, 2 H, C*H*$_2$CH=CH$_2$), 2.09 (s, 3 H, ArCH=CC*H*$_3$), 2.09−1.96 (m, 2 H, C*H*$_2$CH=CH$_2$), 1.74−1.68 (m, 1 H), 1.52−1.43 (m, 2 H), 1.32 (s, 3 H, C(CH$_3$)$_2$), 1.30 (s, 3 H, C(CH$_3$)$_2$), 1.30−1.01 (m, 2 H), 1.02 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$CH(C=O)), 0.79 (d, *J* = 6.5 Hz, 3 H, C*H*$_3$CHCH$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 217.3, 165.1, 164.7, 152.4, 150.4, 139.0, 136.8, 133.2, 121.6, 121.0, 117.8, 116.4, 114.3, 78.5, 74.9, 51.5, 41.5, 37.5, 35.4, 34.1, 32.1, 26.0, 23.2, 23.0, 19.2, 15.5, 14.7, 10.2; HRMS (FAB) calcd for $C_{28}H_{41}$-$CsNO_4S$ (M + Cs$^+$) 620.1811, found 620.1838.

Hydroxy Lactone 37. Olefin Metathesis of Diene 35. A solution of diene **35** (58 mg, 0.12 mmol) in CH_2Cl_2 (129 mL, 0.001 M) was treated with bis(tricyclohexylphosphine)benzylideneruthenium dichloride (RuCl$_2$(=CHPh)(PCy$_3$)$_2$, 10 mg, 0.0012 mmol, 0.1 equiv), in accordance with the procedure described for the synthesis of hydroxy lactone **25**, to furnish, after column chromatography (silica gel, 15% EtOAc in hexanes) hydroxy lactone **37** (48 mg, 86%).

Hydroxy Lactone 38. Olefin Metathesis of Diene 36. A solution of diene **36** (167 mg, 0.34 mmol) in CH_2Cl_2 (340 mL, 0.001 M) was treated with bis(tricyclohexylphosphine)benzylideneruthenium dichloride (RuCl$_2$(=CHPh)(PCy$_3$)$_2$, 28 mg, 0.034 mmol, 0.1 equiv), in accordance with the procedure described for the synthesis of hydroxy lactone **25**, to furnish, after column chromatography (silica gel, 20% EtOAc in hexanes), hydroxy lactone **38** (103 mg, 66%): R_f = 0.38 (silica gel, 30% EtOAc in hexanes); $[\alpha]^{22}_D$ +70.4 (*c* 1.60, $CHCl_3$); IR

(film) ν_{max} 2933, 1703, 1640, 1292, 1179, 982 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 6.97 (s, 1 H, ArH), 6.55 (s, 1 H, ArCH=CCH_3), 6.02 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.51 (dd, J = 8.0, 2.5 Hz, 1 H, CO_2CH), 5.47 (ddd, J = 15.0, 7.5, 7.5 Hz, 1 H, CH=$CHCH_2$), 5.38 (ddd, J = 15.0, 7.5, 7.5 Hz, 1 H, CH=$CHCH_2$), 3.60 (d, J = 6.8 Hz, 1 H, $CHOH(CHCH_3)$), 3.14 (dq, J = 7.0, 7.0 Hz, 1 H, CH_3CH(C=O)), 2.70 (s, 3 H, CH_3Ar), 2.48−2.37 (m, 2 H, CH=$CHCH_2$), 2.21−2.12 (m, 1 H, CH=$CHCH_2$), 2.08 (s, 3 H, ArCH=CCH_3), 1.98−1.90 (m, 1 H, CH=$CHCH_2$), 1.62−1.52 (m, 1 H), 1.41−1.32 (m, 2H), 1.36 (s, 3 H, $C(CH_3)_2$), 1.21 (s, 3 H, $C(CH_3)_2$), 1.17−1.07 (m, 1H), 1.14 (d, J = 7.0 Hz, 3 H, CH_3CH-(C=O)), 0.98−0.87 (m, 1H), 0.97 (d, J = 7.0 Hz, 3 H, CH_3CHCH_2); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 215.5, 165.0, 164.6, 152.2, 150.9, 137.4, 133.6, 126.0, 121.9, 119.4, 115.6, 76.6, 76.2, 51.6, 44.1, 37.9, 36.2, 33.3, 29.6, 27.1, 24.0, 23.0, 18.9, 17.0, 15.9, 15.4; HRMS (FAB) calcd for $C_{26}H_{38}NO_4S$ (M + H$^+$) 460.2522, found 460.2534.

Epothilones 39−41. Epoxidation of *trans*-Hydroxy Lactone 37. Procedure A: A solution of *trans*-hydroxy lactone **37** (20 mg, 0.06 mmol) in $CHCl_3$ (1 mL, 0.06 M) was treated with 3-chloroperoxybenzoic acid (*m*CPBA, 57−86%, 15 mg, 0.05−0.07 mol, 0.9−1.2 equiv) at −20 °C, and the reaction mixture was allowed to warm to 0 °C. After 12 h, disappearance of starting material was detected by TLC, and the reaction mixture was treated with saturated aqueous $NaHCO_3$ solution (2 mL). The aqueous phase was then extracted with EtOAc (3 × 2 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by preparative thin-layer chromatography (250 μm silica gel plate, 30% EtOAc in hexanes) furnished epothilones **39** (or **40**) (12 mg, 40%), **40** (or **39**) (7.5 mg, 25%), and **41** (5.4 mg, 18%). **Procedure B**: To a solution of *trans*-hydroxy lactone **37** (32 mg, 0.07 mmol) in acetonitrile (1.0 mL) was added a 0.0004 M aqueous solution of disodium salt of ethylenediaminetetraacetic acid (Na_2EDTA, 0.5 mL), and the reaction mixture was cooled to 0 °C. Excess of 1,1,1-trifluoroacetone (0.2 mL) was added, followed by a portionwise addition of Oxone (200 mg, 0.35 mmol, 5.0 equiv) and $NaHCO_3$ (50 mg, 0.56 mmol, 8.0 equiv) with stirring, until the disappearance of starting material was detected by TLC. The reaction mixture was then treated with excess dimethyl sulfide (150 μL) and water (1.0 mL) and extracted with EtOAc (4 × 2 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by preparative thin-layer chromatography (250 μm silica gel plate, 70% EtOAc in hexanes) provided a mixture of diastereomeric epoxides, epoxide **39** (or **40**) (15 mg, 45%) and α-isomeric epoxide **40** (or **39**) (9.2 mg, 28%).

Epothilones 42−44. Epoxidation of *trans*-Hydroxy Lactone 38. Procedure A: A solution of *trans*-hydroxy lactone **38** (32 mg, 0.07 mmol) in $CHCl_3$ (1.4 mL) was reacted with 3-chloroperoxybenzoic acid (*m*CPBA, 57−86%, 17.8 mg, 0.06−0.09 mmol, 0.9−1.3 equiv), according to procedure A described for the epoxidation of **37**, resulting in the isolation of epoxides **42** (or **43**) (7.3 mg, 22%), **43** (or **42**) (3.7 mg, 11%), and **44** (2.2 mg, 7%) (stereochemistry unassigned for all compounds), along with unreacted starting material (3.5 mg, 11%), after two consecutive preparative thin-layer chromatographic purifications (250 μm silica gel plate, ether). **Procedure B**: As described in procedure B for the epoxidation of *trans*-hydroxy lactone **37**, *cis*-hydroxy lactone **38** (24 mg, 0.05 mmol) in MeCN (800 μL) was treated with a 0.0004 M aqueous solution of disodium salt of ethylenediaminetetraacetic acid (Na_2EDTA, 380 μL), 1,1,1-trifluoroacetone (150 μL), Oxone (144 mg, 0.25 mmol, 5.0 equiv), and $NaHCO_3$ (36 mg, 0.40 mmol, 8.0 equiv), to yield, after purification by preparative thin-layer chromatography (250 μm silica gel plate, ether), epoxides **42** (or **43**) (15 mg, 60%) and **43** (or **42**) (3.8 mg, 15%). **42** (or **43**): R_f = 0.60 (silica gel, ether); $[\alpha]^{22}_D$ +78.5 (*c* 0.94, $CHCl_3$); IR (film) ν_{max} 3500, 2929, 1714, 1644, 1462, 1293, 1179, 982 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (s, 1 H, ArH), 6.89 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 6.58 (s, 1 H, ArCH=CCH_3), 6.06 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.69 (d, J = 11.0 Hz, 1 H, CO_2CH), 3.80−3.73 (m, 1 H, $CHOH$-$(CHCH_3)$), 3.11 (dq, J = 7.0, 7.0 Hz, 1 H, CH_3CH(C=O)), 2.82−2.74 (m, 2 H), 2.71 (s, 3 H, CH_3Ar), 2.43 (d, J = 14.5 Hz, 1 H), 2.11 (s, 3 H, ArCH=CCH_3), 1.93−1.85 (m, 1 H), 1.60−0.98 (m, 7 H), 1.46 (s, 3 H, $C(CH_3)_2$), 1.24 (s, 3 H, $C(CH_3)_2$), 1.14 (d, J = 7.0 Hz, 3 H, CH_3-CH(C=O)), 1.01 (d, J = 7.0 Hz, 3 H, CH_3CHCH_2); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 212.7, 165.0, 164.7, 152.0, 151.7, 137.0, 121.1, 120.6, 116.7, 76.2, 75.7, 58.7, 57.7, 52.2, 44.4, 37.3, 36.1, 33.5, 30.0, 24.2, 23.0, 22.1, 19.3, 18.1, 14.9, 14.5; HRMS (FAB) calcd for $C_{26}H_{37}NO_5S$ (M + H$^+$) 476.2471, found 476.2485. **43** (or **42**): R_f = 0.64 (silica gel, ether); $[\alpha]^{22}_D$ +38.0 (*c* 0.20, $CHCl_3$); IR (film) ν_{max} 3479, 2926, 2855, 1721, 1702, 1643, 1455, 1174 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 7.01 (s, 1 H, ArH), 6.63 (s, 1 H, ArCH=CCH_3), 6.05 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.47 (dd, J = 7.6, 2.6 Hz, 1 H, CO_2CH), 3.65 (dd, J = 6.5, 3.5 Hz, 1 H, $CHOH(CHCH_3)$), 3.19 (dq, J = 6.8, 6.8 Hz, 1 H, CH_3CH(C=O)), 2.85−2.80 (m, 1 H), 2.78−2.72 (m, 1 H), 2.73 (s, 3 H, CH_3Ar), 2.52 (ddd, J = 15.0, 8.5, 4.0 Hz, 1 H), 2.10 (s, 3 H, ArCH=CCH_3), 1.73 (ddd, J = 15.0, 7.5, 3.5 Hz, 1 H), 1.65−0.80 (m, 7 H), 1.43 (s, 3 H, $C(CH_3)_2$), 1.26 (s, 3 H, $C(CH_3)_2$), 1.15 (d, J = 6.8 Hz, 3 H, CH_3CH-(C=O)), 0.99 (d, J = 7.0 Hz, 3 H, CH_3CHCH_2); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 215.1, 165.5, 164.7, 152.1, 152.0, 130.9, 128.8, 120.9, 115.9, 75.7, 75.2, 57.6, 55.6, 51.7, 44.3, 37.5, 34.4, 32.3, 31.1, 23.9, 23.3, 22.8, 18.8, 17.2, 15.8, 14.6; HRMS (FAB) calcd for $C_{26}H_{37}NO_5S$ (M + H$^+$) 476.2471, found 476.2489. **44**: R_f = 0.60 (silica gel, ether); $[\alpha]^{22}_D$ +23.3 (*c* 0.06, $CHCl_3$); IR (film) ν_{max} 3443, 2924, 1731, 1462, 1260 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (s, 1 H, ArH), 6.84 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 6.04 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.51−5.43 (m, 1H, CH=$CHCH_2$), 5.42−5.35 (m, 1H, CH=$CHCH_2$), 5.05 (dd, J = 10.0, 2.5 Hz, 1 H, CO_2CH), 4.18 (s, 1H, ArCH-O(epoxide)CCH_3), 3.60−3.57 (m, 1 H, $CHOH(CHCH_3)$), 3.06 (dq, J = 7.0, 7.0 Hz, 1 H, CH_3CH(C=O)), 2.72 (s, 3 H, CH_3Ar), 2.56−2.50 (m, 1 H), 2.40−2.32 (m, 1 H), 2.30−2.22 (m, 1 H), 2.14−1.96 (m, 2 H), 1.60−0.98 (m, 4 H), 1.38 (s, 3H, ArCH−O(epoxide)CCH_3), 1.30 (s, 3 H, $C(CH_3)_2$), 1.22 (s, 3 H, $C(CH_3)_2$), 1.14 (d, J = 7.0 Hz, 3 H, CH_3CH(C=O)), 0.95 (d, J = 7.0 Hz, 3 H, CH_3CHCH_2); HRMS (FAB) calcd for $C_{26}H_{38}NO_5S$ (M + H$^+$) 476.2471, found 476.2492.

Hydroxy Keto Acids 45 and 46. Aldol Condensation of Keto Acid 8 and Aldehyde 7. In accordance with the procedure described for the synthesis of keto acids **33** and **34**, keto acid **8** (0.896 g, 2.97 mmol, 1.0 equiv) in THF (10 mL) was treated with lithium diisopropylamide [LDA; freshly prepared from *n*-BuLi (4.36 mL, 1.6 M solution in hexanes, 7.41 mmol, 2.5 equiv) and diisopropylamine (960 μL, 6.83 mmol, 2.3 equiv) in THF (30 mL)] and aldehyde **7** (0.68 g, 5.3 mmol, 1.8 equiv) in THF (30 mL) to afford a mixture of aldol products **45** and **46** in high yield and in a ca. 3:2 ratio (^{1}H NMR), along with unreacted keto acid **8** (5%): R_f = 0.20 (silica gel, 50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$; only signals for **45** and **46** are reported) δ 5.88−5.73 (m, 1 H, CH_2CH=CH_2), 5.04−4.92 (m, 2 H, CH_2CH=CH_2), 4.51−4.47 (m, 0.4 H, $(CH_3)_2CCH$(OTBS)), 4.44−4.40 (m, 0.6 H, $(CH_3)_2CCH$(OTBS)), 3.42 (d, J = 8.0 Hz, 0.4 H, $CHOH$-$(CHCH_3)$), 3.32 (d, J = 9.0 Hz, 0.6 H, $CHOH(CHCH_3)$), 3.30−3.20 (m, 1 H, CH_3CH(C=O), 2.51−2.45 (m, 1 H, CH_2COOH), 2.38 (dd, J = 16.5, 6.5 Hz, 0.4 H, CH_2COOH), 2.35 (dd, J = 16.5, 6.5 Hz, 0.6 H, CH_2COOH), 2.11−1.98 (m, 2 H), 1.80−1.21 (m, 5 H), 1.20 (s, 1.8 H, $C(CH_3)_2$), 1.19 (s, 1.2 H, $C(CH_3)_2$), 1.16 (s, 1.8 H, $C(CH_3)_2$), 1.14 (s, 1.2 H, $C(CH_3)_2$), 1.06 (d, J = 6.5 Hz, 1.2 H), 1.05 (d, J = 6.5 Hz, 1.8 H), 1.00 (d, J = 6.5 Hz, 1.2 H), 0.89 (s, 5.4 H, $SiC(CH_3)_3(CH_3)_2$), 0.87 (s, 3.6 H, $SiC(CH_3)_3(CH_3)_2$), 0.85 (d, J =7.0 Hz, 1.8 H), 0.11 (s, 1.8 H, $SiC(CH_3)_3(CH_3)_2$), 0.09 (s, 1.2 H, $SiC(CH_3)_3(CH_3)_2$), 0.08 (s, 1.2 H, $SiC(CH_3)_3(CH_3)_2$), 0.07 (s, 1.8 H, $SiC(CH_3)_3(CH_3)_2$); HRMS (FAB) calcd for $C_{23}H_{44}NaO_5Si$ (M + Na$^+$) 451.2856, found 451.2867.

Hydroxy Esters 4 and 47. EDC Coupling of Carboxylic Acids 45 and 46 and Alcohol 6. The crude mixture of keto acids **45** and **46** (1.30 g), 4-dimethylaminopyridine (4-DMAP, 0.037 g, 0.3 mmol), and alcohol **6** (1.90 g, 9.0 mmol) in CH_2Cl_2 (5 mL) was treated with 1-ethyl-3-((dimethylamino)propyl)carbodiimide hydrochloride (EDC, 0.7 g, 3.6 mmol), according to the procedure described for the synthesis of keto ester **22a**, producing pure hydroxy esters **4** (0.940 g, 52% from keto acid **8**) and **47** (0.569 g, 31% from keto acid **8**) after flash column chromatography (silica gel, 18% EtOAc in hexanes). **4**: R_f = 0.30 (silica gel, 18% EtOAc in hexanes); $[\alpha]^{22}_D$ −53.4 (*c* 1.00, MeOH); IR (film) ν_{max} 3508, 2932, 1737, 1690, 1650, 1178, 1088, 835 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.93 (s, 1 H, ArH), 6.47 (s, 1 H, ArCH=CCH_3), 5.81−5.73 (m, 1 H, CH_2CH=CH_2), 5.73−5.65 (m, 1 H, CH_2CH=CH_2), 5.27 (dd, J = 7.0, 6.5 Hz, 1 H, CO_2CH), 5.09 (d, J = 17.5 Hz, 1 H, CH_2CH=CH_2), 5.03 (d, J = 10.0 Hz, 1 H, CH_2CH=CH_2), 4.96 (d, J = 17.0 Hz, 1 H, CH_2CH=CH_2), 4.89 (d, J = 10.5 Hz, 1 H, CH_2CH=CH_2), 4.39 (dd, J = 6.0, 4.0 Hz, 1 H, $(CH_3)_2$-CCH(OTBS)), 3.42 (bs, 1 H, CHOH(CHCH$_3$)), 3.28 (q, J = 7.0 Hz, 1

H, $CH_3CH(C{=}O)$), 3.24 (d, J = 9.5 Hz, 1 H, $CHOH(CHCH_3)$), 2.67 (s, 3 H, CH_3Ar), 2.54−2.43 (m, 2 H), 2.43 (dd, J = 10.0, 4.0 Hz, 1 H, CH_2COO), 2.31 (dd, J = 10.0, 6.0 Hz, 1 H, CH_2COO), 2.04 (s, 3 H, $ArCH{=}CCH_3$), 2.03−1.90 (m, 2 H, $CH_2CH{=}CH_2$), 1.75−1.65 (m, 1 H), 1.48−1.43 (m, 1 H), 1.43−1.36 (m, 1 H), 1.22−1.10 (m, 2 H), 1.17 (s, 3 H, $C(CH_3)_2$), 1.09 (s, 3 H, $C(CH_3)_2$), 1.01 (d, J = 6.5 Hz, 3 H, $CH_3CH(C{=}O)$), 0.86 (s, 9 H, $SiC(CH_3)_3(CH_3)_2$), 0.81 (d, J = 7.0 Hz, 3 H, CH_3CHCH_2), 0.09 (s, 3 H, $SiC(CH_3)_3(CH_3)_2$), 0.04 (s, 3 H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 221.8, 170.9, 164.6, 152.4, 139.0, 136.6, 133.2, 121.0, 117.8, 116.4, 114.1, 78.8, 74.5, 73.4, 53.9, 41.2, 40.1, 37.4, 35.4, 34.1, 32.3, 26.0, 25.9, 21.9, 19.9, 19.2, 18.1, 15.2, 14.6, 9.7, −4.3, −4.9; HRMS (FAB) calcd for $C_{34}H_{57}CsNO_5SSi$ (M + Cs^+) 752.2781, found 752.2760. **47**: R_f = 0.20 (silica gel, 18% EtOAc in hexanes); $[\alpha]^{22}_D$ −27.3 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3509, 2932, 2857, 1737, 1691, 1465, 1381, 1292, 1253, 1177, 1088, 984, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.95 (s, 1 H, ArH), 6.49 (s, 1 H, $ArCH{=}CCH_3$), 5.83−5.69 (m, 2 H, 2 x $CH_2CH{=}CH_2$), 5.29 (dd, J = 6.5, 6.5 Hz, 1 H, CO_2CH), 5.11 (d, J = 17.0 Hz, 1 H, $CH_2CH{=}CH_2$), 5.05 (d, J = 10.0 Hz, 1 H, $CH_2CH{=}CH_2$), 5.01 (d, J = 17.0 Hz, 1 H, $CH_2CH{=}CH_2$), 4.95 01 (d, J = 10.5 Hz, 1 H, $CH_2CH{=}CH_2$), 4.50 (dd, J = 6.5, 4.0 Hz, 1 H, $(CH_3)_2CCH(OTBS)$), 3.42 (dd, J = 8.0, 1.5 Hz, 1 H, $CHOH(CHCH_3)$), 3.21 (qd, J = 7.0, 2.0 Hz, 1 H, $CH_3CH(C{=}O)$), 2.70 (s, 3 H, CH_3Ar), 2.54−2.33 (m, 4 H), 2.11−1.98 (m, 2 H), 2.07 (s, 3 H, $ArCH{=}CCH_3$), 1.53−0.98 (m, 5 H), 1.15 (s, 3 H, $C(CH_3)_2$), 1.11 (s, 3 H, $C(CH_3)_2$), 1.01 (d, J = 7 Hz, 3 H, $CH_3CH(C{=}O)$), 0.99 (d, J = 6.5 Hz, 3 H, CH_3CHCH_2), 0.86 (s, 9 H, $SiC(CH_3)_3(CH_3)_2$), 0.08 (s, 3 H, $SiC(CH_3)_3(CH_3)_2$), 0.07 08 (s, 3 H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 220.8, 170.9, 164.4, 152.2, 138.6, 136.6, 133.1, 120.9, 117.8, 116.3, 114.5, 78.8, 74.8, 72.5, 53.9, 41.3, 40.1, 37.4, 35.2, 33.7, 32.0, 25.9, 25.8, 21.7, 19.6, 19.1, 18.1, 15.4, 14.5, 10.5, −4.4, −4.8; HRMS (FAB) calcd for $C_{34}H_{58}NO_5SSi$ (M + H^+) 620.3805, found 620.3813.

. Hydroxy Lactones 3 and 48. Cyclization of Triene 4 *via* Olefin Metathesis. A solution of diene **4** (0.186 g, 0.3 mmol) in CH_2Cl_2 (200 mL, 0.0015 M) was treated with bis(tricyclohexylphosphine)benzylideneruthenium dichloride ($RuCl_2(=CHPh)(PCy_3)_2$, 25 mg, 0.03 mol, 0.1 equiv), for 20 h, in accordance with the procedure described for the synthesis of hydroxy lactone **25**, producing hydroxy lactones **3** (83 mg, 46%) and **48** (70 mg, 39%) after flash chromatography (7 → 25% EtOAc in hexanes). **3**: R_f = 0.18 (silica, 20% EtOAc in hexanes); $[\alpha]^{22}_D$ −79.5 (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 3422, 2930, 1739, 1688, 1255, 1180, 1090, 598 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.96 (s, 1 H, ArH), 6.55 (s, 1 H, $ArCH{=}CCH_3$), 5.45 (ddd, J = 10.5, 10.5, 3.0 Hz, 1 H, $CH{=}CHCH_2$), 5.35 (ddd, J = 10.5, 10.5, 5.5 Hz, 1 H, $CH{=}CHCH_2$), 5.03 (d, J = 10.0 Hz, 1 H, CO_2CH), 4.06 (t, J =6.0 Hz, 1 H, $(CH_3)_2CCH(OTBS)$), 3.94 (bs, 1 H, $CHOH(CHCH_3)$), 3.05 (qd, J =6.5, 3.5 Hz, 1 H, $CH_3CH(C{=}O)$), 3.00 (bs, 1 H, $CHOH(CHCH_3)$), 2.80 (d, J = 6.0 Hz, 2 H, CH_2COO), 2.78−2.69 (m, 1 H), 2.70 (s, 3 H, CH_3Ar), 2.40−2.30 (m, 1 H), 2.10 (s, 3 H, $ArCH{=}CCH_3$), 2.12−2.03 (m, 1 H), 2.00−1.93 (m, 1 H), 1.80−1.74 (m, 1 H), 1.70−1.58 (m, 1 H), 1.50−1.43 (m, 1 H), 1.30−1.15 (m, 2 H), 1.17 (s, 6 H, $C(CH_3)_2$), 1.14 (d, 3 H, J = 5.0 Hz, $CH_3CH(C{=}O)$), 1.02 (d, 3 H, J = 5.0 Hz, CH_3CHCH_2), 0.82 (s, 9 H, $SiC(CH_3)_3(CH_3)_2$), 0.12 (s, 3 H, $SiC(CH_3)_3(CH_3)_2$), −0.05 (s, 3 H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 217.7, 170.7, 164.4, 152.2, 138.1, 134.5, 124.0, 119.5, 116.0, 79.0, 76.3, 73.2, 53.6, 43.1, 39.1, 38.9, 33.7, 32.0, 28.5, 28.0, 26.3, 24.9, 23.0, 19.3, 18.7, 16.6, 15.4, 14.3, −3.4, −5.3; HRMS (FAB) calcd for $C_{32}H_{53}CsNO_5SSi$ (M + Cs^+) 724.2468, found 724.2466. **48**: R_f = 0.40 (silica, 20% EtOAc in hexanes); $[\alpha]^{22}_D$ −71.5 (*c* 0.80, $CHCl_3$); IR (film) ν_{max} 3381, 2958, 2928, 1727, 1273, 1122, 1072 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.00 (s, 1 H, ArH), 6.62 (s, 1 H, $ArCH{=}CCH_3$), 5.36 (ddd, J = 15.0, 7.3, 7.3 Hz, 1 H, $CH{=}CHCH_2$), 5.27 (ddd, J = 15.0, 7.3, 7.3 Hz, 1 H, $CH{=}CHCH_2$), 5.19 (dd, J = 6.5, 3.6 Hz, 1 H, CO_2CH), 4.43 (dd, J = 8.6, 2.7 Hz, 1 H, $(CH_3)_2CCH(OTBS)$), 3.87−3.83 (m, 1 H, $CHOH(CHCH_3)$), 3.29 (bs, 1 H, $CHOH(CHCH_3)$), 3.19 (qd, J = 6.9, 5.4 Hz, 1 H, $CH_3CH(C{=}O)$), 2.71 (s, 3 H, CH_3Ar), 2.72−2.67 (m, 1 H), 2.65 (dd, J = 15.4, 8.6 Hz, 1 H, CH_2COO), 2.59 (dd, J = 15.4, 2.7 Hz, 1 H, CH_2COO), 2.45−2.37 (m, 1 H), 2.20−2.12 (m, 1 H), 2.08 (s, 3 H, $ArCH{=}CCH_3$), 2.00−1.93 (m, 1 H), 1.65−1.44 (m, 4 H), 1.22 (d, 3 H, J = 6.9 Hz, $CH_3CH(C{=}O)$), 1.2−1.12 (m, 1 H), 1.15 (s, 3 H, $C(CH_3)_2$), 1.09 (s, 3 H, $C(CH_3)_2$), 1.03 (d, 3 H, J = 6.9 Hz, CH_3CHCH_2), 0.86 (s, 9 H, $SiC(CH_3)_3(CH_3)_2$), 0.08 (s, 3 H, $SiC(CH_3)_3(CH_3)_2$), 0.00 (s, 3 H, $SiC(CH_3)_3(CH_3)_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 217.9, 169.9, 164.7, 152.1, 136.3, 134.5, 124.9, 119.4, 115.4, 77.4, 75.1, 74.1, 54.1, 43.9, 41.0, 38.5, 35.3, 33.0, 30.9, 27.0, 26.2, 23.8, 21.7, 19.1, 18.5, 17.0, 16.1, 14.8, −3.8, −4.2; HRMS (FAB) calcd for $C_{32}H_{53}CsNO_5SSi$ (M + Cs^+) 724.2468, found 724.2479.

***cis*-Dihydroxy Lactone 49. Desilylation of Compound 3.** Silyl ether **3** (30 mg, 0.05 mmol) was treated with a freshly prepared solution of 20% (v/v) trifluoroacetic acid−CH_2Cl_2 (0.3 mL, 0.17 M) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h (completion of the reaction by TLC), and the solvents were evaporated under reduced pressure. The crude reaction mixture was purified by preparative thin-layer chromatography (0.5 mm silica gel plate, 50% EtOAc in hexanes) to obtain *cis*-dihydroxy lactone **49** (22 mg, 90%): R_f = 0.30 (silica gel, 50% EtOAc in hexanes); $[\alpha]^{22}_D$ −80.2 (*c* 1.36, $CHCl_3$); IR (thin film) ν_{max} 3453, 2929, 1733, 1686, 1506, 1464, 1250, 978 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.95 (s, 1 H, ArH), 6.59 (s, 1 H, $ArCH{=}C(CH_3)$), 5.44 (ddd, J = 10.5, 10.5, 4.5 Hz, 1 H, $CH{=}CHCH_2$), 5.36 (ddd, J = 10.5, 10.5, 5.0 Hz, 1 H, $CH{=}CHCH_2$), 5.28 (d, J = 9.4 Hz, 1 H, CO_2CH), 4.23 (d, J = 11.1 Hz, 1 H, $(CH_3)_2CCH(OH)$), 3.72 (m, 1 H, $CHOH(CHCH_3)$), 3.43−3.37 (m, 1 H, OH), 3.14 (q, J = 6.7 Hz, 1 H, $CH_3CH(C{=}O)$), 3.05 (bs, 1 H, OH), 2.72−2.63 (m, 1 H), 2.69 (s, 3 H, CH_3Ar), 2.48 (dd, J = 14.8, 11.3 Hz, 1 H, CH_2COO), 2.33 (dd, J = 14.8, 2.0 Hz, 1H, CH_2COO), 2.30−2.13 (m, 2 H) 2.07 (s, 3 H, $ArCH{=}CCH_3$), 2.07−1.98 (m, 1 H), 1.80−1.60 (m, 2H), 1.32 (s, 3 H, $C(CH_3)_2$), 1.36−1.13 (m, 3 H), 1.17 (d, J = 6.8 Hz, 3 H, $CH_3CH(C{=}O)$), 1.06 (s, 3 H, $C(CH_3)_2$), 0.99 (d, J = 7.0 Hz, 3 H, CH_3CHCH_2); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 220.6, 170.4, 165.0 151.9, 138.7, 133.4, 125.0, 119.4, 115.8, 78.4, 74.1, 72.3, 53.3, 41.7, 39.2, 38.5, 32.4, 31.7, 27.6, 27.4, 22.7, 19.0, 18.6, 15.9, 15.5, 13.5; HRMS (FAB) calcd for $C_{26}H_{39}CsNO_5S$ (M + Cs^+) 610.1603, found 610.1580.

***trans*-Dihydroxy Lactone 50. Desilylation of Compound 48.** Silyl ether **48** (32 mg, 0.05 mmol) was treated with a freshly prepared solution of 20% (v/v) trifluoroacetic acid (TFA)−CH_2Cl_2 (0.3 mL, 0.17 M), according to the procedure described for *cis*-dihydroxy lactone **49**, to yield, after preparative thin-layer chromatography (0.5 mm silica gel plate, 50% EtOAc in hexanes), *trans*-dihydroxy ester **50** (24 mg, 92%): R_f = 0.15 (silica gel, 50% EtOAc in hexanes); $[\alpha]^{22}_D$ −62.7 (*c* 1.65, $CHCl_3$); IR (film) ν_{max} 3428, 2932, 1730, 1692, 1468, 1253, 976 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.97 (s, 1 H, ArH), 6.56 (s, 1 H, $ArCH{=}CCH_3$), 5.49 (ddd, J = 15.0, 4.7, 4.7 Hz, 1 H, $CH{=}CHCH_2$), 5.38 (dd, J = 5.7, 5.7 Hz, 1 H, CO_2CH), 5.37 (ddd, J = 15.0, 6.5, 6.5 Hz, 1 H, $CH{=}CHCH_2$), 4.18 (d, J = 10.5 Hz, 1 H, $(CH_3)_2CCH(OH)$), 3.73 (m, 1 H, $CHOH(CHCH_3)$), 3.27−3.20 (m, 2 H, $CH_3CH(C{=}O)$ and OH), 2.82 (bs, 1 H, OH), 2.70 (s, 3 H, CH_3Ar), 2.55 (dd, J = 15.5, 10.5 Hz, 1 H, CH_2COO), 2.48−2.43 (m, 3 H), 2.18−2.12 (m, 1 H), 2.07 (s, 3 H, $ArCH{=}CCH_3$), 1.98−1.91 (m, 1 H), 1.63−1.55 (m, 2 H), 1.46 (dddd, J = 12.5, 12.5, 4.0, 4.0 Hz, 1 H), 1.27 (s, 3 H, $C(CH_3)_2$), 1.23−1.14 (m, 2 H), 1.17 (d, J = 6.5 Hz, 3 H, $CH_3CH(C{=}O)$), 1.06 (s, 3 H, $C(CH_3)_2$), 0.97 (d, J = 6.5 Hz, 3 H, CH_3CHCH_2); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 219.8, 170.4, 164.9, 151.9, 137.1, 134.2, 125.6, 119.6, 115.9, 77.5, 75.7, 72.2, 52.5, 43.5, 38.8, 37.6, 36.1, 32.3, 31.2, 26.9, 21.3, 21.1, 19.1, 17.0, 15.7, 14.3; HRMS (FAB) calcd for $C_{26}H_{40}NO_5S$ (M + H^+) 478.2627, found 478.2612.

Epothilones A (1) and 51−57. Epoxidation of *cis*-Dihydroxy Lactone 49. Procedure A: A solution of *cis*-dihydroxy lactone **49** (24 mg, 0.05 mmol) in $CHCl_3$ (4.0 mL) was reacted with 3-chloroperoxybenzoic acid (*m*CPBA, 57−86%, 13.0 mg, 0.04−0.06 mmol, 0.8−1.2 equiv), at −20 → 0 °C, according to the procedure described for the epoxidation of **37**, resulting in the isolation of epothilone A (**1**) (8.6 mg, 35%), its isomeric α-epoxide **51** (2.8 mg, 13%), and compounds **52** (or **53**) (1.6 mg, 9%), **53** (or **52**) (1.5 mg, 7%), **54** (or **55**) (1.0 mg, 5%), and **55** (or **54**) (1.0 mg, 5%) (stereochemistry unassigned for **52** and **53** and for **54** and **55**); after two consecutive preparative thin-layer chromatographic purifications (250 μm silica gel plate, 5% MeOH in CH_2Cl_2 and 70% EtOAc in hexanes). **Procedure B:** To a solution of *cis*-dihydroxy lactone **49** (15 mg, 0.03 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C was added dropwise a solution of dimethyldioxirane in acetone (ca. 0.1 M, 0.3 mL, ca. 1.0 equiv) until no starting lactone was detectable by TLC. The solution was then concentrated in vacuo and the crude product was subjected to two consecutive preparative thin-layer chromatographic purifications (250 μm silica gel

plate, 5% MeOH in CH_2Cl_2 and 70% EtOAc in hexanes), to obtain pure epothilone A (**1**) (7.4 mg, 50%), its isomeric α-epoxide **51** (2.3 mg, 15%), and epothilones **52** (or **53**) (0.8 mg, 5%) and **53** (or **52**) (0.8 mg, 5%) (stereochemistry unassigned for **52** and **53**. **Procedure C**: As described in procedure B for the epoxidation of *trans*-hydroxy lactone **37**, *cis*-dihydroxy lactone **49** (10.0 mg, 0.02 mmol) in MeCN (200 μL) was treated with a 0.0004 M aqueous solution of disodium salt of ethylenediaminetetraacetic acid (Na_2EDTA, 120 μL), excess 1,1,1-trifluoroacetone (100 μL), Oxone (61 mg, 0.10 mmol, 5.0 equiv), and $NaHCO_3$ (14 mg, 0.16 mmol, 8.0 equiv), to yield, after purification by preparative thin-layer chromatography (250 μm silica gel plate, ether), a mixture of diastereomeric epoxides, epothilones A (**1**) (6.4 mg, 62%) and α-isomeric epoxide **51** (1.3 mg, 13%). **Procedure D**: A solution of *cis*-dihydroxy lactone **49** (18 mg, 0.037 mmol) in $CHCl_3$ (1.0 mL) was treated with 3-chloroperoxybenzoic acid (*m*CPBA, 57–86%, 15 mg, 0.049–0.074 mmol, 1.3–2.0 equiv), according to the procedure described for the epoxidation of **37**, furnishing compounds **1** (2.7 mg, 15%), **51** (1.8 mg, 10%), **52** (or **53**) (1.8 mg, 10%), **53** (or **52**) (1.4 mg, 8%), **54** (or **55**) (1.4 mg, 8%), **55** (or **54**) (1.26 mg, 7%), **56** (0.9 mg, 5%), and **57** (0.9 mg, 5%) (stereochemistry unassigned for **52**–**57**), after two consecutive preparative thin-layer chromatographic purifications (250 μm silica gel plate, 5% MeOH in CH_2Cl_2 and 70% EtOAc in hexanes). Epothilone A (**1**): $R_f = 0.23$ (silica gel, 33% MeOH–CH_2Cl_2); HPLC (Watman EOC, C-18, 4 μ, 108 × 4.6 mm column, solvent gradient: 0 → 20 min, 30 → 80% MeOH in H_2O) $R_t = 14.8$ min; $[\alpha]_D = -45.0$ (*c* 0.02, MeOH); IR (film) ν_{max} 3476, 2974, 1738, 1692 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ = 6.71 (s, 1 H, ArC*H*=CCH_3), 6.45 (s, 1 H, ArH), 5.45 (dd, 1 H, *J* = 8.2, 2.3 Hz, CO_2CH), 4.15 (dd, 1 H, *J* = 10.8, 2.9 Hz, $(CH_3)_2CCH(OH)$), 3.81–3.78 (m, 1 H, *CH*OH($CHCH_3$)), 3.65 (bs, 1 H, OH), 3.03 (qd, *J* = 6.9, 6.5 Hz, 1 H, $CH_3CH(C{=}O)$), 2.77 (ddd, *J* = 7.9, 4.0, 4.0 Hz, 1 H, CH_2CH-O(epoxide)CH), 2.62–2.58 (m, 1 H, CH_2CH-O(epoxide)CH), 2.40 (dd, *J* = 14.4, 10.8 Hz, 1 H, CH_2COO), 2.26 (bs, 1 H, OH), 2.21 (s, 3 H, CH_3Ar), 2.19 (dd, *J* = 14.4, 2.9 Hz, 1 H, CH_2COO), 2.05 (s, 3 H, ArCH=CCH_3), 1.86 (ddd, *J* = 15.2, 2.5, 2.5 Hz, 1 H, CH_2CH–O(epoxide)CH), 1.81–1.74 (m, 1 H, CH_2CH–O(epoxide)CH), 1.68 (ddd, *J* = 15.2, 7.6, 7.6 Hz, 1 H, CH_2CH–O(epoxide)CH), 1.53–1.49 (m, 1 H, CH_2CH–O(epoxide)CH), 1.40–1.15 (m, 5 H), 1.06 (d, 3 H, *J* = 7.0 Hz, $CH_3CH(C{=}O)$), 1.03 (s, 3 H, $C(CH_3)_2$), 0.97 (s, 3 H, $C(CH_3)_2$), 0.95 (d, *J* = 6.9 Hz, 3 H, CH_3CHCH_2); ^{13}C NMR (150.9 MHz, C_6D_6) δ 219.0, 170.2, 164.7, 153.0, 137.5, 119.9, 116.6, 76.6, 75.2, 73.5, 57.2, 54.2, 52.9, 43.8, 39.1, 36.3, 31.7, 30.3, 27.3, 23.9, 21.1, 20.6, 18.7, 17.4, 15.7, 14.6; HRMS (FAB) calcd for $C_{26}H_{39}CsNO_6S$ (M + Cs^+) 626.1552, found 626.1531. **51**: $R_f = 0.35$ (silica gel, 70% EtOAc in hexanes); $[\alpha]^{22}_D$ −23.0 (*c* 0.10, $CHCl_3$); IR (film) ν_{max} 3416, 2925, 2855, 1732, 1688, 1457 1258, 1150 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.79 (s, 1 H, ArC*H*=CCH_3), 6.57 (s, 1 H, ArH), 5.82 (d, *J* = 8.0 Hz, 1 H, CO_2CH), 4.31 (dd, *J* = 10.5, 2.5 Hz, 1 H, $(CH_3)_2CCH(OH)$), 4.19–4.15 (m, 1 H, *CH*OH($CHCH_3$)), 3.78 (bs, 1 H), 3.31 (qd, *J* = 7.0, 3.0 Hz, 1 H, $CH_3CH(C{=}O)$), 2.82 (ddd, *J* = 10.0, 4.2, 4.2 Hz, 1 H, CH_2CH-O(epoxide)CH), 2.76 (bs, 1 H), 2.55 (ddd, *J* = 9.0, 9.0, 4.5 Hz, 1 H, CH_2CH-O(epoxide)CH), 2.40 (dd, *J* = 13.0, 10.5, 1 H, CH_2COO), 2.33 (dd, *J* = 13.0, 2.5 Hz, 1 H, CH_2COO), 2.31 (s, 3 H, CH_3Ar), 2.20 (s, 3 H, ArCH=CCH_3), 1.97–1.92 (m, 1 H), 1.72 (ddd, *J* = 15.0, 8.5, 8.5 Hz, 1 H), 1.56 (ddd, *J* = 15.0, 4.5, 2.0 Hz, 1 H), 1.54–1.28 (m, 6 H), 1.17 (d, *J* = 7.0 Hz, 3 H, $CH_3CH(C{=}O)$), 1.13 (s, 3 H, $C(CH_3)_2$), 1.06 (d, *J* = 7.0 Hz, 3 H, CH_3CHCH_2), 0.97 (s, 3 H, $C(CH_3)_2$); ^{13}C NMR (150.9 MHz, C_6D_6) δ 221.7, 171.0, 165.5, 154.2, 138.3, 120.7, 117.6, 77.0, 74.8, 73.2, 57.7, 56.8, 52.4, 43.5, 39.5, 38.5, 33.0, 31.4, 28.3, 24.6, 21.6, 19.5, 19.2, 17.0, 15.7, 13.9; HRMS (FAB) calcd for $C_{26}H_{40}NO_6S$ (M + H^+) 494.2576, found 494.2558.

Oxidation of Epothilone A (1) with *m*CPBA. A solution of epothilone A (**1**) (3.0 mg, 0.006 mmol) in $CHCl_3$ (120 μL, 0.05 M) was reacted with 3-chloroperoxybenzoic acid (*m*CPBA, 57–86%, 1.1 mg, 0.0023–0.0032 mmol, 0.8–1.1 equiv), at −20 → 0 °C, according to the procedure described for the epoxidation of **37**, resulting in the formation of bis(epoxides) **54** (or **55**) (1.1 mg, 35%) and **55** (or **54**) (1.0 mg, 32%) along with sulfoxide **57** (0.2 mg, 6%).

Epothilones 58–60. Epoxidation of *trans*-Dihydroxy Lactone 50. Procedure A: A solution of *trans*-dihydroxy lactone **50** (20 mg, 0.042 mmol) in $CHCl_3$ (4.0 mL) was treated with 3-chloroperoxybenzoic acid (*m*CPBA, 57–86%, 11.0 mg, 0.036–0.054 mmol, 0.9–1.3 equiv) at −20 → 0 °C, according to the procedure described for the epoxidation of compound **37**, to give a epothilones **58** (1.0 mg, 5%), **59** (1.0 mg, 5%), and **60** (12 mg, 60%) (stereochemistry unassigned for all three), after preparative thin-layer chromatography (250 μm silica gel plate, 70% EtOAc in hexanes). **Procedure B**: According to procedure B for the epoxidation of *cis*-dihydroxy lactone **49**, a solution of *trans*-dihydroxy lactone **50** (10.0 mg, 0.02 mmol) in CH_2Cl_2 (1.0 mL) was reacted with a solution of dimethyldioxirane (ca. 0.1 M, 0.2 mL, ca. 1.0 equiv) in acetone at 0 °C, and after preparative thin-layer chromatography (250 μm silica gel plate, 70% EtOAc in hexanes), epothilones **58** (1.0 mg, 10%), **59** (1.0 mg, 10%), and **60** (4.0 mg, 40%) were obtained. **Procedure C**: As described in procedure B for the epoxidation of *trans*-hydroxy lactone **37**, *trans*-dihydroxy lactone **50** (5.1 mg, 0.01 mol) in MeCN (100 μL) was treated with a 0.0004 M aqueous solution of disodium salt of ethylenediaminetetraacetic acid (Na_2EDTA, 60 μL), excess 1,1,1-trifluoroacetone (100 μL), Oxone (32 mg, 0.05 mmol, 5.0 equiv), and $NaHCO_3$ (7.0 mg, 0.08 mmol, 8.0 equiv), to yield, after purification by preparative thin-layer chromatography (250 μm silica gel plate, ether), epothilones **58** (2.3 mg, 45%) and **59** (1.8 mg, 35%). **58**: $R_f = 0.15$ (silica gel, ether); $[\alpha]^{22}_D$ −23.3 (*c* 0.40, $CHCl_3$); IR (film) ν_{max} 3454, 2926, 2856, 1731, 1690, 1464, 1376, 1259, 1151, 980 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.73 (s, 1 H, ArC*H*=$C(CH_3)$), 6.53 (s, 1 H, ArH), 5.54 (dd, *J* = 8.0, 2.0 Hz, 1 H, CO_2CH), 4.18 (d, *J* = 10.0 Hz, 1 H, $(CH_3)_2CCH(OH)$), 3.87 (dd, *J* = 4.5, 2.0 Hz, 1 H, *CH*OH($CHCH_3$)), 3.43 (bs, 1 H), 3.13 (dq, *J* = 7.0, 7.0 Hz, 1 H, $CH_3CH(C{=}O)$), 2.74–2.72 (m, 1 H), 2.63–2.60 (m, 1 H), 2.45 (dd, *J* = 15.0, 10.5 Hz, 1 H, CH_2COO), 2.33 (dd, *J* = 15.0, 3.0 Hz, 1 H, CH_2COO), 2.32–2.24 (m, 1 H), 2.28 (s, 3 H, CH_3Ar), 2.12 (s, 3 H, ArCH=CCH_3), 2.00 (ddd, *J* = 15.0, 3.0, 2.5 Hz, 1 H), 1.75–1.65 (m, 3 H), 1.60–0.98 (m, 4 H), 1.18 (d, *J* = 7.0 Hz, 3 H, $CH_3CH(C{=}O)$), 1.10 (s, 3 H, $C(CH_3)_2$), 1.05 (s, 3 H, $C(CH_3)_2$), 0.97 (d, *J* = 7.0 Hz, 3 H, CH_3CHCH_2); ^{13}C NMR (125.7 MHz, C_6D_6) δ 217.2, 170.3, 164.6, 153.2, 137.0, 120.4, 116.9, 76.7, 75.6, 72.8, 58.0, 56.0, 53.0, 44.7, 38.8, 36.5, 35.8, 32.0, 30.3, 30.1, 22.6, 21.0, 20.9, 17.1, 15.3, 14.9; HRMS (FAB) calcd for $C_{25}H_{39}CsNO_6S$ (M + Cs^+) 626.1552, found 626.1538. **59**: $R_f = 0.20$ (silica gel, ether); $[\alpha]^{22}_D$ −25.3 (*c* 0.30, $CHCl_3$); IR (film) ν_{max} 3419, 2923, 1732, 1691, 1464, 1259 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.82 (s, 1 H, ArC*H*=$C(CH_3)$), 6.56 (s, 1 H, ArH), 5.53 (dd, *J* = 7.5, 3.5 Hz, 1 H, CO_2CH), 4.47 (d, *J* = 8.5 Hz, 1 H, $(CH_3)_2CCH(OH)$), 3.94 (bs, 1 H, *CH*OH-($CHCH_3$)), 3.65–3.58 (m, 1 H), 3.35 (dq, *J* = 6.5, 6.5 Hz, 1 H, $CH_3CH(C{=}O)$), 2.73–2.65 (m, 1 H), 2.65–2.61 (m, 1 H), 2.52–2.46 (m, 1 H), 2.41 (dd, *J* = 14.0, 9.5 Hz, 1 H, CH_2COO), 2.33 (dd, *J* = 14.0, 4.0 Hz, 1 H, CH_2COO), 2.31 (s, 3 H, CH_3Ar), 2.03 (s, 3 H, ArCH=CCH_3), 1.91–1.81 (m, 2 H), 1.78–1.53 (m, 4 H), 1.41–1.32 (m, 2 H), 1.22 (d, *J* = 7.0 Hz, 3 H, $CH_3CH(C{=}O)$), 1.21 (s, 3 H, $C(CH_3)_2$), 1.08 (d, *J* = 7.0 Hz, 3 H, CH_3CHCH_2), 1.05 (s, 3 H, $C(CH_3)_2$); ^{13}C NMR (150.9 MHz, C_6D_6) δ 215.7, 167.6, 161.7, 149.8, 133.8, 116.6, 113.4, 73.8, 73.2, 70.1, 55.2, 52.4, 49.9, 41.7, 36.4, 34.0, 32.3, 28.0, 27.8, 27.4, 19.9, 17.8, 15.8, 14.6, 13.0, 12.3; HRMS (FAB) calcd for $C_{26}H_{39}CsNO_6S$ (M + Cs^+) 626.1552, found 626.1531. **60**: $R_f = 0.6$ (silica gel, 70% EtOAc in hexanes); $[\alpha]^{22}_D$ −28.3 (*c* 0.30, $CHCl_3$); IR (film) ν_{max} 3472, 2928, 1735, 1691, 1466 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.67 (s, 1 H, ArH), 5.48–5.41 (m, 1 H, *CH*=$CHCH_2$), 5.36–5.23 (m, 2 H, *CH*=$CHCH_2$ and CO_2CH), 4.36–4.30 (m, 1 H, $(CH_3)_2CCH(OH)$), 3.79–3.73 (m, 1 H), 3.63–3.58 (m, 1 H), 3.17–3.10 (m, 1 H, $CH_3CH(C{=}O)$), 2.81 (bs, 1 H), 2.53 (dd, *J* = 15.0, 10.5 Hz, 1 H, CH_2COO), 2.40–2.29 (m, 2 H), 2.26–2.19 (m, 2 H), 2.25 (s, 3 H, CH_3Ar), 2.20–1.95 (m, 1 H), 1.80–1.72 (m, 1 H), 1.62–1.53 (m, 1 H), 1.46–1.33 (m, 2 H), 1.20 (d, *J* = 6.5 Hz, 3 H, $CH_3CH(C{=}O)$), 1.13 (s, 3 H, $C(CH_3)_2$), 1.10 (s, 3 H, $C(CH_3)_2$), 1.08 (d, *J* = 7.0 Hz, 3 H, CH_3CHCH_2), 1.06 (s, 3 H, ArCH–O(epoxide)-CCH_3); ^{13}C NMR (125.7 MHz, C_6D_6) δ 219.7, 169.6, 166.9, 151.3, 135.4, 124.6, 115.8, 78.3, 72.8, 72.6, 64.2, 59.1, 53.3, 43.4, 40.2, 38.8, 34.3, 33.1, 31.4, 27.5, 21.8, 19.8, 18.9, 16.5, 15.3, 14.0; HRMS (FAB) calcd for $C_{26}H_{40}NO_6S$ (M + H^+) 494.2576, found 494.2587.

Dihydroxy Ester 61. Desilylation of Compound 47. Silyl ether **47** (48 mg, 0.079 mmol) was treated with a freshly prepared solution of 20% (v/v) trifluoroacetic acid (TFA)–CH_2Cl_2 (1.6 mL, 0.05 M), according to the procedure described for the desilylation of compound

3, to yield, after flash column chromatography (silica gel, 5% → 50% EtOAc in hexanes), dihydroxy ester **61** (35 mg, 90%).

Dihydroxy Lactones 62 and 63. Olefin Metathesis of Dihydroxy Ester 61. A solution of compound **61** (48 mg, 0.095 mmol) in CH_2Cl_2 (20 mL, 0.005 M) was treated with bis(tricyclohexylphosphine)-benzylideneruthenium dichloride ($RuCl_2(=CHPh)(PCy_3)_2$, 16 mg, 0.019 mmol, 0.2 equiv), according to the procedure described for the cyclization of **25**, producing dihydroxy lactones **62** (9.1 mg, 20%) and **63** (32 mg, 69%), after preparative thin-layer chromatograpy (0.5 mm silica gel plate, 33% EtOAc in hexanes).

Epothilones 64−65. Epoxidation of *cis*-Dihydroxy Lactone 62. Procedure A: A solution of *cis*-dihydroxy lactone **62** (10.0 mg, 0.021 mmol) in $CHCl_3$ (210 μL) was treated with 3-chloroperoxybenzoic acid (*m*CPBA, 57−86%, 5.0 mg, 0.0165−0.0252 mmol, 0.8−1.2 equiv) at −20 → 0 °C, according to the procedure described for the epoxidation of compound **37**, to produce, after preparative thin-layer chromatography (250 μm silica gel plate, 70% EtOAc in hexanes), epothilones **64** (or **65**)(2.6 mg, 25%) and **65** (or **64**) (2.4 mg, 23%) (stereochemistry unassigned for all three). **Procedure B:** As described in procedure B for the epoxidation of *trans*-hydroxy lactone **37**, *cis*-dihydroxy lactone **62** (10.0 mg, 0.021 mmol) in MeCN (400 μL) was treated with a 0.0004 M aqueous solution of disodium salt of ethylenediaminetetraacetic acid (Na_2EDTA, 200 μL), excess 1,1,1-trifluoroacetone (150 μL), Oxone (65 mg, 0.105 mmol, 5.0 equiv), and $NaHCO_3$ (14 mg, 0.168 mmol, 8.0 equiv), to yield, after purification by preparative thin-layer chromatography (250 μm silica gel plate, ether), epothilones **64** (or **65**) (6.0 mg, 58%) and **65** (or **64**) (3.0 mg, 29%).

Epothilones 67−69. Epoxidation of *trans*-Dihydroxy Lactone 63. Procedure A: A solution of *trans*-dihydroxy lactone **63** (17.0 mg, 0.033 mmol) in $CHCl_3$ (2.0 mL) was treated with 3-chloroperoxybenzoic acid (*m*CPBA, 57−86%, 8.9 mg, 0.029−0.044 mmol, 0.9−1.3 equiv) at −20 → 0 °C, according to the procedure described for the synthesis of epoxide **37**, to produce, after preparative thin-layer chromatography (250 μm silica gel plate, 70% EtOAc in hexanes), epothilones **67** (or **68**) (4.2 mg, 24%), **68** (or **67**) (3.3 mg, 19%), and **69** (5.4 mg, 31%) (stereochemistry unassigned for all three). **Procedure B:** As described in procedure C for the epoxidation of *cis*-lactone **49**, *trans*-dihydroxy lactone **63** (6.0 mg, 0.0126 mmol) in MeCN (240 μL) was treated with a 0.0004 M aqueous solution of disodium salt of ethylenediaminetetraacetic acid (Na_2EDTA, 90 μL), 1,1,1-trifluoroacetone (90 μL), Oxone (40 mg, 0.063 mmol, 5.0 equiv), and $NaHCO_3$ (8.4 mg, 0.100 mmol, 8.0 equiv), to yield, after purification by preparative thin-layer chromatography (250 μm silica gel plate, ether), epothilones **67** (or **68**) (2.7 mg, 44%) and **68** (or **67**) (1.3 mg, 21%).

Acknowledgment. We thank Dr. G. Höfle for an authentic sample of natural epothilone A (**1**) and Drs. Raj Chada, Dee H. Huang, and Gary Siuzdak for their superb X-ray crystallographic, NMR, and mass spectroscopic assistance, respectively. This work was financially supported by The Skaggs Institute for Chemical Biology, the National Institutes of Health USA, fellowships from Novartis (D.V.), the Deutsche Forschungsgemeinschaft (DFG) (F.R.), the Fundación Ramón Areces (F.S.), and the National Science Foundation (NSF) (J.I.T.), and grants from Amgen, DuPont-Merck, Hoffmann La Roche, Merck, Schering-Plough, and CaPCURE.

Supporting Information Available: Selected physical properties for compounds of **17b**, **18b**, **22b**, **29−32**, **37**, **39−41**, **52−57**, and **61−69**, X-ray crystallographic parameters for compound **28**, and $^1H-^1H$ NOESY and $^1H-^1H$ COSY NMR spectra for **58** and **59** (39 pages). See any current masthead page for ordering and Internet access instructions.

JA9711091